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HYPERCALCEMIA WITHOUT HYPERCALCURIA OR HYPOPHOSPHATEMIA, CALCINOSIS AND RENAL INSUFFICIENCY*

A Syndrome Following Prolonged Intake of Milk and Alkali

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BOSTON AND BALTIMORE

BECAUSE of our interest in the parathyroid glands our attention has been directed to a number of diseases with which primary hyperparathyroidism may be confused. These include acute osteoporosis,[1] hypervitaminosis D,[2-4] sarcoidosis,[5, 6] myelomatosis,[6-8] carcinomatosis with extensive bone involvement,[6] polyostotic fibrous dysplasia,[9] renal osteitis fibrosa generalisata[10] and osteomalacia.[10] By clinical and laboratory observations it is usually possible to differentiate these conditions from primary hyperparathyroidism. However, when the latter condition is complicated by secondary renal damage the diagnosis, in our experience, may be very difficult.[6, 11] This report describes a syndrome observed in 6 patients that has many features in common with primary hyperparathyroidism and secondary kidney damage but that we now believe has an entirely different etiology.

The characteristic features in these patients are a history of prolonged and excessive intake of milk and absorbable alkali; hypercalcemia without hypercalcuria or hypophosphatemia; normal serum alkaline phosphatase level; marked renal insufficiency with azotemia; mild alkalosis; calcinosis manifested especially by an ocular lesion resembling band keratitis; and an improvement in the clinical state on an intake low in milk and absorbable alkali.

CASE REPORTS

CASE 1. A. McA. (M. G. H. 235557), a 44-year-old caretaker, was first admitted to the hospital in February, 1940, complaining of pruritus of 3 years' duration. Since the age of 11, he had suffered from epigastric pain relieved by food and sodium bicarbonate. Three years before admission, a peptic ulcer had been found on x-ray examination; subsequently, he had been almost constantly on a regimen of several quarts of milk daily and large quantities of absorbable alkalis. Five years before admission, during a period of 3 months, he had had three attacks of renal colic with passage of gravel and stones. On a high fluid intake there had been no recurrence of these symptoms. Other significant points in the past history were spinal meningitis at the age of 21, and a heavy alcoholic intake for 30 years.

Physical examination disclosed a well developed and well nourished man. The corneas showed band keratopathy; the fundi were normal. The liver edge was just felt at the costal margin. The blood pressure was 140/80.

Routine urinalyses revealed a maximal specific gravity of 1.012, acid reactions and a ++ test for albumin. The sediment contained 10 to 15 white cells per high-power field, an occasional red cell and rare granular casts; urine culture was negative. The phenolsulfonephthalein test demonstrated 15 per cent excretion of the dye 1 hour after intravenous injection. The Sulkowitch test showed no increase in calcium. A test for urinary Bence-Jones protein was negative. Examination of the blood disclosed a red-cell count of 4,350,000, with a hemoglobin of 85 per cent, and a white-cell count of 9700, with a normal differential. There were no abnormal cells in the sternal bone marrow. The serum calcium was 12.4 mg., inorganic phosphorus 4.0 mg., alkaline phosphatase 5.3 Bodansky units, and nonprotein nitrogen 58 mg. per 100 cc. The carbon dioxide combining power was 27.4 milliequiv. per liter, and the protein 9.8 gm. per 100 cc.

A gastrointestinal series revealed a nonobstructing duodenal ulcer. Films of the skull showed normal bones.

A definite diagnosis was not made, but the patient was discharged on a reduced milk intake and advised to take no alkalis.

On his second and third admissions, both in October, 1941, he complained of great weakness, continuing pruritus, polydipsia and polyuria. The ulcer had been asymptomatic, milk intake had averaged 2 or 3 glasses daily, and he had taken no alkalis. The physical examination revealed no changes from the previous admission. Examination of the urine was unchanged. The serum calcium was 12.0 to 14.6 mg., and the phosphorus 4.0 to 4.7 mg. per 100 cc. The alkaline phosphatase was 1.7 Bodansky units, the carbon dioxide content 31 milliequiv. and the chloride 84.5 milliequiv. per liter. The nonprotein nitrogen was 80 mg., and the total protein 9.2 mg. per 100 cc., with an albumin of 5.6 gm. and a globulin of 3.6 gm. Calcium and phosphorus balance was negative. The average urinary excretion of calcium was 87 mg. per 24 hours.

Further x-ray studies demonstrated no evidence of decalcification in the skeleton. The lamina dura about the teeth was preserved.

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An exploration for parathyroid adenoma was carried out. Three parathyroid glands were located, which on biopsy proved to be normal.

During the next 2 years the patient again remained on a low calcium intake and took no alkali. He re-entered the hospital in June, 1942, because of bleeding from the duodenal ulcer. Laboratory studies were essentially the same as those on previous admissions, with the addition of a serum sodium of 135 milliequiv. per liter. A plain x-ray film of the abdomen showed small kidneys and areas of calcification in the lower pole of the left kidney.

The fifth admission, in October, 1943, was for another episode of bleeding from the ulcer. Urinalysis demonstrated a ++++ test for albumin. The serum calcium was 10.1 mg., the phosphorus 10 mg., and the total protein 8.6 gm. per 100 cc.; the chloride was 71.7 milliequiv., and the carbon dioxide content 25.6 milliequiv. per liter. X-ray films of the bones were normal.

The final admission was in April, 1944, terminating in death from renal insufficiency. Laboratory studies performed shortly before death revealed a serum calcium of 7.7 mg. and a phosphorus of 9.4 mg. per 100 cc., a phosphatase of 18.0 Bodansky units and a chloride of 84 milliequiv., a sodium of 128 milliequiv. and a carbon dioxide content of 9.5 milliequiv. per liter. The nonprotein nitrogen was 150 mg. and the total protein 7.87 gm. per 100 cc., with 5.17 gm. of albumin and 2.70 gm. of globulin.

The diagnoses at autopsy were as follows: chronic pyelonephritis; nephrocalcinosis; calcification of the dura mater, diaphragm, costal cartilages, tendons and blood vessels; bronchopneumonia of all lobes; gastric ulcer, well healed; and prostatic abscess. No parathyroid glands were found, but it is not known whether a careful search for them was made.

There had been no urinary symptoms except nocturia, (twice) for about 2 years. Urinalysis 20 months before admission had shown a slight trace of albumin.

Physical examination revealed a very emaciated young man with marked atrophy of the skin and muscles. The eyes were prominent, and the corneas demonstrated changes consistent with band keratopathy. The fundi were normal. The skin was dry and scaly, with brownish pigmentation over some of the keratotic areas. The blood pressure was 88/70.

Routine urinalysis disclosed a maximal specific gravity of 1.008 and a +++ test for albumin, with a pH 6.5 to 7.5. The sediment contained white cells, frequently in clumps, and occasional granular casts. Urine cultures showed a moderate growth of *Staphylococcus aureus* and colon bacilli in one, and no growth in another; phenolsulfonephthalein excretion was 3 per cent in 1 hour. The Sulkowitch test demonstrated no calcium. A test for Bence-Jones protein was negative. The urinary 17-ketosteroid excretion was 2.7 and 3.0 mg. per 24 hours.

Examination of the blood revealed a red-cell count of 2,250,000 with a hemoglobin of 45 per cent, and a white-cell count of 8500, with a normal differential. There was marked variation in the size and shape of the erythrocytes. The serum calcium was 12.0 to 12.8 mg., the alkaline phosphatase 2.8 to 6.8 Bodansky units, the protein 7.1 gm., the nonprotein nitrogen 85 mg., the cholesterol 184 mg., and the fasting blood sugar 83 mg. per 100 cc. The carbon dioxide combining power was 23.3 to 30.2 milliequiv., and the chloride 89 to 95 milliequiv. per liter. The basal metabolic rate was −6 per cent. In the sternal bone marrow there was no evidence of leukemia or multiple myeloma.

A gastrointestinal series gave no evidence of disease. X-ray films of the long bones showed extensive periosteal new bone formation about the humeri, radii, metacarpals, pelvis, femora, tibias, fibulas, tarsals, and metatarsals. Films of the skull demonstrated extensive calcification of the tentorium, the falx and the dura over the cerebral hemispheres. In the chest there was extensive calcification of the bronchial tree. On a plain film of the abdomen, the kidneys were poorly outlined but appeared smaller than normal, without unusual areas of calcification within them.

On a low calcium diet the serum calcium fell to 11.2 mg., and the nonprotein nitrogen to 40 mg. per 100 cc; the phosphorus, chloride and carbon dioxide combining power did

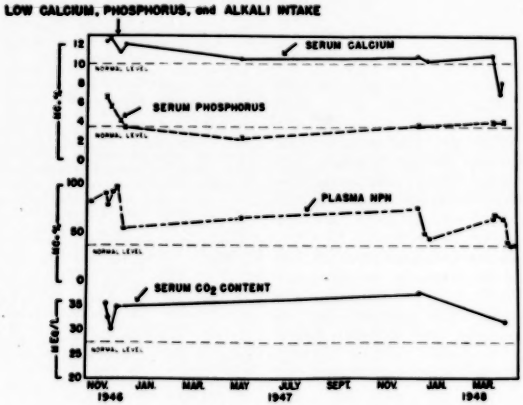

FIGURE 1. *Laboratory Findings in Case 3.*

CASE 2. A. C. (M. G. H. 267258), a 25-year-old man, first entered the hospital in September, 1940, complaining of vomiting and eructations for 2 1/2 years. Epigastric pain relieved by food and soda had started while he was a senior in college and worrying about examinations. A milk and alkali regimen was prescribed, and until his admission, because of persistent gastrointestinal symptoms, he was almost constantly on such a program. He had lost 50 pounds since the onset of his illness. Repeated x-ray films of the gastrointestinal tract were reported to have shown no abnormalities.

not change. Symptomatically he was slightly improved on discharge.

He was not seen again at the Massachusetts General Hospital, failed progressively after discharge and died in July, 1943. No autopsy was performed, and the nature of the terminal illness is unknown.

CASE 3. C. McC. (M. G. H. 324826), a 44-year-old married man, was first seen in October, 1941, complaining of intermittent claudication. A diagnosis of thromboangiitis obliterans was made, and a left lumbar sympathectomy performed. Three routine urine specimens were entirely normal; the specific gravities varied between 1.002 and 1.014. A bi-

and duodenitis. The bones of the hands and skull were normal. In the abdomen there was extensive calcification of both iliac arteries and calcification in the region of both kidneys, probably in the renal arteries, and in the aorta.

On a low calcium diet and high fluid intake the patient was much better subjectively, and the pruritus diminished remarkably. Coincident with the clinical improvement the serum calcium fell to 11.4 mg. and the nonprotein nitrogen to 52 mg. per 100 cc.

In May, 1947, on a follow-up visit, the serum calcium was 10.6 mg., the phosphorus 2.3 mg., and the nonprotein nitrogen 64 mg. per 100 cc. During several visits between December, 1947, and February, 1948, the serum nonprotein ni-

TABLE 1. *Summary of Renal-Function Tests.*

CASE NO.	DATE	GLOMERULAR FILTRATION*	EFFECTIVE PLASMA FLOW	MAXIMAL TUBULAR EXCRETORY CAPACITY	FILTRATION FRACTION	RATIO OF GLOMERULAR FILTRATION TO MAXIMAL TUBULAR EXCRETORY CAPACITY	PHENOLSULFONEPHTHALEIN EXCRETION	STANDARD UREA CLEARANCE
		cc./1.73 sq. m/min.	*cc./1.73 sq. m/min.*	*mg./1.73 sq. m/min.*			%	%
1	—	—	—	—	—	—	5 (in 15 min.)	—
							20 (in 2 hr.)	
2	—	—	—	—	—	—	3 (in 1 hr.)	—
3	—	41	141	6.3	0.29	6.5	—	—
4	—	—	—	—	—	—	8 (in 30 min.)	25
5	9/10/47	—	—	—	—	—	5 (in. 1 hr.)	—
	8/19/47	20	48	2.5	0.42	8.0	—	—
	5/27/48	21	60	4.0	0.35	5.2	—	—
6	1/19/48	34	136	17.1	0.25	2.0	10 (in 2 hr.)	—
	3/29/48	40	172	—	0.22	—	—	—
Normal values		130	700	75.0	0.19	1.7	—	—

*Glomerular filtration rates were measured with mannitol in Cases 4 and 5, and with inulin in Case 6. Effective plasma flow and maximal tubular excretory capacity were determined with sodium para-amino hippurate. (We are indebted to Dr. W. P. Boger, of Sharp and Dohme, Inc., for generous supplies of mannitol and sodium para-amino hippurate.)

opsy taken from the left kidney at the time of operation revealed normal renal tissue.

The patient had been told 25 years previously that he had a peptic ulcer. Since then, milk and antacids had been frequently employed to control symptoms.

In May, 1943, he entered another hospital in uremia. A serum nonprotein nitrogen of 198 mg. per 100 cc., a low urine specific gravity and a + test for albumin were reported at this time. With parenteral administration of fluids he improved and was discharged.

In November, 1946, the patient again entered the Massachusetts General Hospital because of exacerbation of ulcer symptoms, nervousness, fatigue, nausea and intractable pruritus. He had continued to take large quantities of milk and variable amounts of alkalis.

Physical examination showed a thin, haggard man with a sallow complexion. The eyes disclosed band keratopathy and normal fundi. The only arterial pulsation palpable in either leg was that of the right femoral artery. The left arm and leg were warmer than the right. The blood pressure was 175/105.

Routine urinalysis demonstrated a maximal specific gravity of 1.011, a + + test for albumin and a pH of 6.0 to 7.5. The sediment contained rare hyaline and granular casts and occasional red cells and white cells. Urine cultures revealed a moderate growth of *Staphylococcus albus* and *aureus*, but were negative for pleuropneumonia-like organisms. The urine calcium excretion was 109 mg. per 24 hours. The results of renal-function studies are presented in Table 1.

Examination of the blood showed a red-cell count of 4,050,000, with a hemoglobin of 10 gm., and a white-cell count of 9800, with a normal differential. The serum calcium was 12.4 to 12.8 mg., inorganic phosphorus 5.5 to 6.6 mg., nonprotein nitrogen 90 mg., and alkaline phosphatase 7.2 Bodansky units per 100 cc. The chloride was 90 to 105 milliequiv., per liter, and the carbon dioxide content 30 to 35 milliequiv. per liter, and the total protein 7.7 gm. per 100 cc., with an albumin of 4.96 gm. and a globulin of 2.12 gm. Gastric analysis disclosed 4 units of free and 11 units of combined hydrochloric acid.

A gastrointestinal series gave evidence of an old duodenal ulcer, probably still active, with accompanying gastritis,

trogen was 48 to 75 mg., calcium 10.6 mg., phosphorus 2.0 to 2.3 mg., and alkaline phosphatase 3.0 to 3.4 Bodansky units per 100 cc., and the carbon dioxide content was 37.3 milliequiv. and the chloride 107 milliequiv. per liter. The results of laboratory studies between November, 1946, and February, 1948, are presented in Figure 1. When last seen in February, 1948, the only symptoms were those referable to an obstructing duodenal ulcer. The patient had remained on a low milk and alkali and high fluid regimen since discharge.

CASE 4. T. W. (J. H. H. 204618), a 38-year-old physician, entered the hospital in July, 1940, for surgical therapy of intractable ulcer symptoms. He had had symptoms of peptic ulcer, which had begun while he was in medical school in 1928. There was then a period during which he was relatively asymptomatic until 1937, when symptoms recurred and x-ray examination demonstrated a duodenal ulcer. From this time until admission he took 6 or more teaspoonfuls of sodium bicarbonate and drank 2 or 3 quarts of milk daily. Two years prior to admission nocturia and polyuria had begun and had been increasing. He had never had symptoms of nephrolithiasis.

Physical examination showed normal fundi, with conjunctival crystals and band keratopathy bilaterally. The blood pressure was 140/80.

Routine urinalysis was entirely negative. The urea clearance was 16 per cent of normal. The phenolsulfonephthalein excretion was 8 per cent in the first 1/2 hour, and 28 per cent in 2 hours. The serum nonprotein nitrogen was 78 mg., calcium 12.5 and 12.7 mg., phosphorus 6.5 and 7.3 mg., and protein 6.5 and 6.8 gm. per 100 cc., and the carbon dioxide combining power was 26.8 milliequiv., and the chloride 100 milliequiv. per liter.

A gastrointestinal series demonstrated a duodenal defect characteristic of ulcer.

Parathyroid exploration was carried out on July 10, and enlargement of all four parathyroid glands was found. Three glands and about three quarters of the remaining one were removed. The pathological diagnosis was hyperplasia of the chief and oxyphil types. On July 24 hypercalcemia was still present, the blood calcium determination being 13.5 mg. per 100 cc. The serum phosphorus was 5.9 mg. per 100 cc.

At the next admission, on October 30, the patient felt very much better and had been carrying on an active practice. The serum calcium was 12.2 mg., and the phosphorus 4.5 mg. per 100 cc. The nonprotein nitrogen had fallen to 45 mg. per 100 cc. He now had a secondary anemia that had not been present on the first admission.

When next seen in March, 1942, he was improved in every respect. He had no further symptoms of ulcer, and had remained on a milk-free diet without alkalis. Nocturia had diminished from five times to two times. For 2 months he had noticed tingling in the toes if pressure were made on the posterior aspects of the thighs. Trousseau's sign was positive in 90 seconds, although Chvostek's sign was negative. These symptoms of tetany were relieved by calcium acetate. The conjunctival lesions had partially cleared.

Laboratory studies demonstrated a serum nonprotein nitrogen of 52 mg., calcium of 6.4 mg., phosphorus of 6.4 mg. and protein of 6.0 gm. per 100 cc. The carbon dioxide combining power was 20 milliequiv., and the chloride 107 milliequiv. per liter.

The patient was seen again in 1944, when retinal hemorrhages and narrowing of the retinal arteries had developed. The blood pressure had risen to 150/100. The phenolsulfonephthalein excretion was 10 per cent in the first 30 minutes; the serum nonprotein nitrogen was 64 mg. per 100 cc. The calcium and phosphorus values were unchanged. The blood showed a moderate anemia.

By October, 1946, there was marked progression of the renal disease and evidence of congestive heart failure. The blood pressure was 140/100. The nonprotein nitrogen ranged between 145 and 160 mg. per 100 cc. The serum calcium was 7.5 mg., the phosphorus 7.7 mg., and the protein 5.6 gm. per 100 cc.

The patient died in January, 1947; an autopsy was not performed.

CASE 5.* E. McD. (W. R. V. A. H. 12467), a 55-year-old carpenter, first entered the hospital in September, 1946. One grandmother was an American Indian.

He had had symptoms and x-ray signs suggestive of ulcer since 1930 although a definite x-ray diagnosis had never been made. Treatment had consisted almost continuously of 4 or 5 quarts of milk daily and large quantities of sodium bicarbonate. Hypertension had been noted in 1930. For 5 years he had had nocturia (once or twice,) and dribbling of urination. He had complained of aching of the ankles, knees and hips for 4 years; for 6 months the ankles and lower legs had been swollen. A prominent secondary complaint was severe generalized pruritus. He had never been given vitamin D for his arthritic complaints.

Physical examination revealed an elderly appearing man whose skin was dark brown. Dime-sized, movable, firm, subcutaneous nodules were noted on the extensor surface of the forearms. Examination of the eyes disclosed white plaques on the conjunctivas and crystalline opacities along the medial edge of the corneas; there was tortuosity of the vessels of the fundi and arteriovenous nicking. A Grade II systolic murmur was heard in the aortic area. Edema of the feet, ankles and lower legs was present. The prostate was enlarged. The blood pressure was 150/80.

Routine urinalyses demonstrated a maximal specific gravity of 1.011 and a ++ to +++ test for albumin. The sediment contained occasional white cells and red cells. The phenolsulfonephthalein excretion was 5 per cent in 1 hour. Examination of the blood showed a hemoglobin of 10.0 gm. and a white-cell count of 7100, with a normal differential. The serum calcium was 11 to 14 mg., the phosphorus 4.1 to 5.9 mg., the nonprotein nitrogen 89 to 100 mg., the total protein, 7.6 gm., with 4.68 gm. of albumin and 2.92 gm. of globulin, and the cholesterol 320 to 550 mg. per 100 cc.

A gastrointestinal series was normal. X-ray films revealed cancellous bone and a very dense skull and long bones. The falx, cerebrum and soft tissues of the knees, elbows, hands and lungs were calcified. Retrograde pyelograms disclosed slight clubbing of the calyxes of the kidneys.

An electrocardiogram demonstrated myocardial disease, with right bundle-branch block and auriculoventricular block, probably on the basis of arteriosclerotic heart disease.

The patient was discharged on December 7, on a low protein and low salt diet. During the next 6 months clinically his condition remained essentially unchanged, necessitating three readmissions during April, May and June, of 1947, with the same general complaints. It is questionable whether during this period he adhered to his diet, and hence whether his milk and alkali intake was much reduced.

Between April and July routine urinalyses were unchanged. The urinary calcium was 77.8 and 77 mg. per 24 hours. The results of renal-function studies are presented in Table 1.

Examination of the blood showed a red-cell count of 4,300,000, with a hemoglobin of 73 per cent. The serum nonprotein nitrogen was 90 to 137 mg., the calcium 10.8 to 12.8 mg., the phosphorus 4.2 to 5.4 mg., the alkaline phosphatase 3.2 to 5.9 Bodansky units, and the cholesterol 415 mg. per 100 cc. The chloride was 91 to 101 milliequiv., and the carbon dioxide content 32 milliequiv. per liter. A biopsy of a subcutaneous nodule demonstrated calcified material embedded in large areas of dense fibrous tissue. A bone biopsy revealed dense cortical bone of normal architecture, with granular basophilic deposit in the periphery of the Haversian canals.

From July, 1947, to June, 1948, the patient was maintained on a regimen low in milk, sodium and protein. Subjectively he was somewhat improved, but continued to complain of joint pains, weakness and pruritus. On readmission in June, 1948, the physical findings were unchanged. There was also no change in the urine or in renal function (Table 1). The serum nonprotein nitrogen was 125 mg., the calcium 10.7 mg., and the phosphorus 2.8 mg. per 100 cc.; the chloride was 110 milliequiv., the sodium 138 milliequiv., and the potassium 4.3 milliequiv. per liter. The protein was 7.2 gm. per 100 cc., with 4.39 gm. of albumin and 2.81 gm. of globulin.

He was not seen again in the hospital and died at home in December, 1948. The nature of his terminal illness is unknown. Permission for autopsy was not obtained.

CASE 6. M. J. L. (E. M. H. 329,496), a 54-year-old fireman, was admitted to the hospital in January, 1948, because of hematemesis. Ulcer symptoms had been present for over 30 years, and treatment had almost always included several quarts of milk daily and large quantities of sodium bicarbonate. In November, 1946, the diagnoses of active duodenal ulcer and chronic nephritis had been made at the Massachusetts General Hospital.

The past history revealed a heavy alcoholic intake. Nocturia (up to five times) had been present for 5 years, and mild pruritus for 2 years. The right eye had been removed at the Massachusetts Eye and Ear Infirmary in 1945 because of changes secondary to glaucoma and chorioretinal degeneration.

The blood pressure was 130/70 after the initial hypotension due to blood loss had been relieved. The left cornea showed band keratopathy; the fundus was normal.

Routine urinalyses demonstrated a maximal specific gravity of 1.016, no albumin and a normal sediment. The results of renal-function studies are presented in Table 1. The hemoglobin was 10 gm. per 100 cc. The white-cell count and differential were normal. The stools were guaiac positive during the 1st week of hospitalization. On admission the nonprotein nitrogen was 131 mg., the calcium 11.5 mg., the phosphorus 4.6 mg., and the alkaline phosphatase 4.4 Bodansky units per 100 cc., and the carbon dioxide content was 33 milliequiv., and the chloride 95 milliequiv. per liter.

A gastrointestinal series revealed a duodenal defect consistent with peptic ulcer. An x-ray film of the abdomen disclosed an area of irregular density at the level of the fourth lumbar vertebra, probably representing calcified mesenteric nodes.

The bleeding stopped spontaneously, and the pyloric obstruction was treated with gastric suction. While the patient was on suction considerable alkalosis developed, with a serum carbon dioxide content of 38 milliequiv. per liter and a chloride of 89 milliequiv. per liter. After relief of the obstruction and parenteral administration of physiologic saline solution the serum carbon dioxide content fell to 27 milliequiv., and the serum chloride rose to 106 milliequiv. per liter, and the serum nonprotein nitrogen stabilized at 60 to 80 mg. per 100 cc. He was discharged on a low milk and alkali regimen considerably improved.

In March, 1948, he was readmitted for further renal-function studies. Physical examination was unchanged. Examination of the urine was also unchanged. The results of renal-function tests are presented in Table 1. The serum nonprotein nitrogen was 62 mg., the total protein 4.64 gm.,

*We are indebted to Dr. A. S. Zdanis for asking us to study this patient.

with 3.11 gm. of albumin and 1.54 gm. of globulin, the calcium 10.9 mg., the phosphorus 2.7 mg., and the alkaline phosphatase 3.66 Bodansky units per 100 cc. The carbon dioxide content was 29 milliequiv., the chloride 103 milliequiv., the sodium 135 milliequiv., and the potassium 4.1 milliequiv. per liter.

In June a posterior gastroenterostomy was performed because of recurrent pyloric obstruction. The patient withstood the operation well. Laboratory studies shortly before discharge disclosed a serum nonprotein nitrogen of 71 mg., calcium of 9.1 mg., and phosphorus of 2.7 mg. per 100 cc., with a carbon dioxide content of 29 milliequiv. and a chloride of 96 milliequiv. per liter.

He has remained relatively asymptomatic since discharge.

Clinical Features

The clinical features of these cases are shown in Table 2 and 3. All 6 patients gave a similar history of having suffered symptoms characteristic of peptic ulcer for many years, in excess of ten years with the exception of 1 patient (Case 2), who had had symptoms for only two years. In 4 cases duodenal ulcer was demonstrated by x-ray examination; in a fifth (Case 5) the presence of a peptic ulcer seems almost certain although the diagnosis was never definitely established by x-ray study.

Treatment of each patient had consisted of almost continuous ingestion of large quantities of milk and absorbable alkalis, usually sodium bicarbonate, for periods of a few to many years. Nephrolithiasis had occurred in 1 case several years previously (Case 1). In 2 patients (Cases 5 and 6), there was a history of previous hypertension. In no case was there a history suggestive of preceding acute glomerulonephritis or pyelonephritis.

The primary complaints were exacerbation of ulcer or gastrointestinal symptoms in 4 cases, intractable pruritus in 1 and arthritic complaints in 1. Pruritus was an important secondary complaint in 3 others.

A moderate hypertension was present initially in 5 patients, and as the disease progressed, the physical findings usually became the expected ones of hypertension and renal failure.

Early in the course, the physical finding that was most striking and the only one common to all patients was that found in the eyes (Table 3[12-14]). The ocular lesions were believed to be associated with hypercalcemia from any cause, and have been described in a previous report,[12] which includes Cases 1, 2, 3 and 4 in this series. Cases 1, 2, 3, 5 and 6 will also be included in another report now in press.[13] In brief, these changes are of two types. In one there are corneal changes consisting of hazy, granular and subepithelial deposits running concentrically with the limbus on either the nasal or the temporal side or both. These lesions are similar to band keratitis, but in the opinion of Cogan[13] are not a true keratitis and are better designated as band keratopathy. In the other type of lesion there are small glass-like particles in the conjunctivas of the palpebral-fissure area. Biopsy of this type of lesion in 1 of the cases in the series of Walsh and Howard[12] showed an amorphous material, presumably a calcium salt beneath the conjunctival membrane. In all patients in the present series, band keratopathy was demonstrated; in 2 the conjunctival lesions were also present.

Table 2. *Summary of Clinical and X-Ray Features.*

Features	No. of Cases
Ulcer symptoms for two to thirty years	6
Excessive milk and alkali intake	6
Ocular lesions	6
Renal insufficiency	6
Hypertension	5
Duodenal ulcer by x-ray study	4
Pruritus	4

Table 3. *Abnormalities of Soft Tissues and Bones.*

Case No.	Eyes		Other Soft Tissues	Bones
	Band keratopathy	Conjunctival crystals		
1	+	0	Nephrocalcinosis; calcification of dura mater, diaphragm, costal cartilages, tendons and blood vessels.*	Normal
2	+	0	Extensive calcification of tentorium, falx and dura over cerebral hemispheres, and bronchial tree	Extensive periosteal new bone formation of long bones
3	+	0	Calcification of abdominal blood vessels	Normal
4	+	+	—	Normal
5	+	+	Subcutaneous calcified nodules of elbows,† hands and knees; calcification in lung.	Dense cortical bone†
6	+	0	Calcified mesenteric lymph nodes	Normal

*Autopsy.
†Biopsy.

The combination of elevated serum calcium and a slightly elevated or normal serum phosphorus present in this syndrome theoretically should favor metastatic calcification. In addition to those uniformly present in the eyes, such changes were present elsewhere in 5 of the 6 patients, but they were extremely irregular in their anatomic distribution (Table 3). They varied from widespread soft-tissue calcification (subcutaneous, lungs and falx cerebrum) to a few calcified mesenteric lymph nodes.

In 2 patients significant abnormalities of the bones were demonstrated: extremely dense can-

cellous bone in Case 5, and extensive periosteal new bone formation in Case 2. The bones in the remaining 4 cases were normal.

Four patients have died; the other 2, although they still show evidence of renal insufficiency, remain symptomatically improved.

Laboratory Findings

The laboratory findings are summarized in Table 1 and 4. The biochemical abnormalities in the blood and urine were usually unsuspected and always puzzling. In general they were at first inspection those of advanced renal insufficiency, but with definite differences from the pattern usually seen in uremia.

Table 4. *Summary of Laboratory Findings.*

Finding	No. of Cases
Renal insufficiency	6
Azotemia	
Fixed urinary specific gravity	
Depression of renal-function tests	
Hypercalcemia	5
No hypercalcuria	5
Mild alkalosis	5
Albuminuria	5

Azotemia was always present; the nonprotein nitrogen level varied from 50 to 150 mg. per 100 cc. Under treatment the nitrogen retention usually diminished.

Definite hypercalcemia was present in 5 patients, the serum calcium level varying between 12.0 and 14.5 mg. per 100 cc. In Case 6 only a moderate hypercalcemia was demonstrated (11.2 mg. per 100 cc.) after the patient came under observation. However, in several of the other patients, the serum calcium fell as renal failure progressed. We have assumed that a more severe hypercalcemia had been present in the past in this patient since he showed all the other characteristics of the syndrome.

The serum phosphorus typically was normal or high, varying from 3.0 to 7 mg. per 100 cc. Except for a terminal level of 10 mg. in Case 1, none of the patients ever exhibited the degree of hyperphosphatemia usually present in uremia, nor was the hypophosphatemia of hyperparathyroidism present at the time when the serum calcium was elevated. Another puzzling feature of the syndrome is the fall in serum phosphorus in some cases after withdrawal of milk and alkali. Thus, in Cases 3 and 5, although the serum calcium levels fell from 12.8 and 14 to 10.6 and 10.7 mg. per 100 cc. respectively, the serum phosphorus levels fell from 6.6 and 5.9 to 2.0 and 2.6 mg. per 100 cc. respectively. In Case 5 (in which only moderate hypercalcemia was demonstrated), the serum calcium levels remained at 11.5 and 10.9 mg. per 100 cc., whereas the serum phosphorus levels fell from 4.6 to 2.7 mg. per 100 cc. It appears that the high phosphate, as well as the high calcium content, of milk is a factor in this syndrome.

Urinary calcium excretion was not shown to be increased by quantitative measurements in 3 patients or by the Sulkowitch test in 2.

Instead of the acidosis (as evidenced by low serum carbon dioxide content) usually seen in renal insufficiency, 5 patients had at some time slightly high carbon dioxide contents of the serum, ranging from 30 to 36 milliequiv. per liter. At times this was associated with alkali ingestion and vomiting, but the tendency toward alkalosis occasionally persisted so far as could be determined even after these factors had been removed. In 1 fatal case (Case 1) acidosis eventually developed during the terminal phase of the illness.

The serum protein levels were not so low as might have been expected in view of the degree of renal insufficiency present; indeed, in 3 patients (Cases 1, 3 and 5) actual hyperproteinemia was demonstrated. On fractionation this elevation appeared to be chiefly in the albumin in each case.

Albuminuria was present in all but 1 patient. The urinary sediment contained no abnormal constituents in 2 patients; in the other 4 it contained occasional to rare hyaline and granular casts, infrequent red cells and occasional to many white cells. Urine cultures were negative in 1 patient, grew *Staph. aureus* and *Esch. coli* in 1 and *Staph. aureus* and *albus* in 1, and were not done in 3 patients.

The results of the various renal-function measurements, which are presented in Table 1, indicated advanced renal disease. Ability to concentrate the urine was uniformly absent. From the renal clearances in 3 patients it is apparent that all portions of the nephron were impaired. The high filtration fraction and the high ratio of glomerular filtration rate to maximal tubular excretory capacity suggest relatively greater insufficiency of tubular as compared with glomerular function. The recognized limitations of clearance technics in advanced renal disease, however, render such a conclusion only tentative.

Discussion

The presence of primary hyperparathyroidism was suspected in each of these cases. In 1 patient who died the parathyroid glands were not located at autopsy. This is the same patient (Case 1) in whom three years previously normal parathyroid glands had been found at operation. One other patient (Case 4) who was explored showed parathyroid hyperplasia of the chief and oxyphil cell variety thought to be characteristic of secondary hyperparathyroidism.[15] In the other 4 patients it is admittedly impossible to state that primary hyperparathyroidism was not present in addition to renal failure. We have been led to seek another

explanation because of certain atypical features of the syndrome, no one of which is insurmountable but which taken as a group could hardly be explained by primary hyperparathyroidism. These features are: lack of hypophosphatemia accompanying the hypercalcemia; lack of hypercalcuria; lowering of the serum calcium on a low calcium intake; and absence of skeletal demineralization or its laboratory manifestation, elevation of serum alkaline phosphatase.

Renal failure associated with hypercalcemia in diseases other than hyperparathyroidism has been observed in acute osteoporosis,[1] hypervitaminosis D,[2-4] sarcoidosis,[5, 6] myelomatosis,[6-8] and generalized carcinomatosis with metastatic bone involvement.[6] All these conditions seem to have been adequately excluded in this series. A special search was made in each case for a history of excessive intake of vitamin D; none was elicited.

In chronic Bright's disease with uremia, there are usually hypocalcemia, hyperphosphatemia and metabolic acidosis,[16-18] a very different biochemic pattern from that described above.

The possibility that ulcer regimens employing milk and absorbable alkalis adversely affect kidney function has been suggested repeatedly. There is little question that acute alkalosis may cause a temporary and sometimes marked diminution in renal function, and that a subsequent striking improvement may occur after correction of the alkalosis.[19-22] Some observers have found no evidence of antecedent renal disease in their patients.[23, 24] Definite proof that alkalosis can cause any permanent renal damage is still lacking.[21, 22]

The present series of cases is somewhat different from previously reported ones, in that no episodes of acute alkalosis with accompanying severe dehydration, hypochloremia and azotemia were known to have occurred. All patients were found to be suffering from chronic renal failure, usually incidental to other complaints. In the 2 patients who are still living and in the 3 who died on whom autopsies were not obtained, the histories gave no evidence of previous renal disease, although 2 were known to have had hypertension. The case in which a post-mortem examination was performed showed a renal lesion diagnosed as pyelonephritis and nephrocalcinosis. From this case alone, one might hypothesize that for the production of the syndrome the presence of underlying renal disease is necessary on which is superimposed the harmful effect of milk and alkalies on the kidneys. On the other hand in Case 2 urinalyses were normal, as was a kidney biopsy only two years before renal insufficiency developed, so that there is little evidence of antecedent kidney disease in this case. The final answer clearly must await more extensive observations.

The abnormalities of calcium metabolism as evidenced by calcinosis and hypercalcemia are extremely puzzling, and no complete explanation for them is evident from our data. Hypercalcemia has previously been observed during episodes of acute alkalosis associated with excessive intake of alkalis and calcium.[24, 25] To our knowledge cases of prolonged hypercalcemia and renal failure such as those observed in this series have not been recorded. The absence of hypercalcuria and the lowering of the serum calcium level following low calcium intake suggest an interference with the renal excretion of calcium. The exact mechanism of this interference with excretion cannot even be speculated upon until the normal mechanisms for the renal excretion of calcium are elucidated.

The mechanism of a slight persistent alkalosis after relief of vomiting and withdrawal of alkali is equally difficult to explain. There may have been, of course, vomiting or alkali ingestion of which we were unaware when the high serum carbon dioxide contents were observed, but this explanation seems unlikely. When serum sodium determinations were done they were normal or slightly low, and the alkalosis was not invariably accompanied by hypochloremia. The association of intracellular potassium deficiency and alkalosis suggests itself.[26-28] However, there is no reason to believe that there was such a deficiency in any of these patients, and the serum potassiums when measured were normal.

The observation of high serum proteins with the elevation chiefly in the albumin fraction is also most unusual. They were determined in several different laboratories, by the usual Howe technic, and appear consistent enough to exclude artifacts or errors in measurement.

Each of these patients showed evidence of improvement after institution of low milk, low alkali and high fluid intakes. Subjectively they felt better; chemically, the azotemia diminished in all patients, and hypercalcemia diminished in the 5 cases in which it was demonstrated. This therapeutic response strengthens our conviction that the deranged homeostasis was in some manner associated with the excessive ingestion of milk and alkalis.

Summary

A syndrome observed in 6 male patients, all of whom gave the common history of peptic ulcer or ulcer symptoms treated by excessive intake of milk and alkalis for many years, is described.

The syndrome is characterized by a history of prolonged and excessive intake of milk and absorbable alkali; hypercalcemia without hypercalcuria or hypophosphatemia; normal serum alkaline phosphatase levels; marked renal insufficiency with azotemia; mild alkalosis; calcinosis manifested especially by an ocular lesion resembling band keratitis; and improvement on an intake low in milk and absorbable alkali.

Although primary hyperparathyroidism could not be excluded positively in all patients, the evi-

dence, in our opinion, suggests that the abnormalities observed in the calcium and phosphorus metabolisms were a result of the following sequence of events: excessive intakes of milk (a foodstuff high in calcium and phosphorus) and alkalis; kidney damage; tendency to fixation in urinary calcium excretion; hypercalcemia; tendency to supersaturation in respect to calcium phosphate; and calcinosis. The improvement resulting from a low intake strongly supports this sequence.

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DEATH FROM ATTEMPTED ABORTION WITH A POTASSIUM PERMANGANATE DOUCHE

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ALTHOUGH potassium permanganate is commonly employed as a disinfectant and deodorant and for local application in the treatment of dermatitis, fatal poisoning from its use is rare. As evidence of this, Green and Warr,[1] in reviewing the literature from 1899–1941, were able to find only 8 fatal cases. On the other hand, these authors reported 31 cases in which potassium permanganate was ingested, none of which resulted fatally. Except in children, the poison was invariably swallowed with suicidal intent, since the intense blue color of even a very dilute solution tends to make disguise difficult.

Within recent years, necrotizing injury of the vagina and cervix due to the use of potassium permanganate tablets (0.3 to 1.0 gm.) as an abortifacient has been reported in increasing numbers of cases, mostly from European countries.[2–14] That the practice occurs also in this country has been stressed by McDonough,[15] who reviewed 65 cases, in all of which admission of the use of potassium permanganate as an abortifacient was sooner or later obtained from the patient. Actually, only 6 patients were successful in the attempt to terminate the pregnancy. The chief clinical evidence was bleeding, which usually occurred within two hours of the insertion of the tablet. Although none of the cases reported by McDonough ended fatally, operative intervention by suturing at bleeding sites was necessary in 10 cases, and in 34 others close packing of the vagina for forty-eight hours was necessary to control the hemorrhage. Twelve patients required treatment for shock, with multiple transfusions. There was no evidence of toxemia that was thought to be attributable to systemic absorption of the chemical itself.

The case presented below is the first to our knowledge in which death has occurred after the use of potassium permanganate as an abortifacient. Although the circumstances are unusual in that the abortive procedure consisted in the intravaginal instillation of what was apparently a saturated solution of potassium permanganate containing at

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least 7 gm. of solid potassium permanganate, the post-mortem findings and subsequent investigations are judged to have been of sufficient interest to warrant presentation.

Case Report

A 21-year-old single woman, pregnant for the second time, entered a general hospital in a state of acute collapse with slight to moderate vaginal bleeding and brownish staining of the perineum. Death occurred about 8 hours later. The total duration of illness was said to have been about 12 hours. The history given by her sister, a nurse, was that the decedent had attempted abortion by douching herself with a solution of potassium permanganate. This solution is said to have been prepared by the addition of about 2 ounces of permanganate crystals to 3 ounces of water.*

Post-mortem examination, conducted 6 hours after death, showed the body of a well developed and well nourished woman of about the stated age. The entire skin surface was a uniform, light-mahogany brown, although prior to the fatal illness, it was learned, the skin had appeared a normal white. The uterus could be palpated as a soft freely movable intra-abdominal mass extending from the pubis almost to the umbilicus. There was focal and confluent superficial hemorrhagic necrosis of intravaginal cervical epithelium, and a small amount of liquid blood oozed from the dilated cervical canal.

On internal examination, the principal abnormalities were to be found in the soft and boggy uterus, which measured 18 by 14 by 10 cm. and showed a diffusely hyperemic serosal surface. The cervix was soft and flattened in its infero-superior aspect. The os was dilated to about 1.0 cm. in diameter. Upon opening, the inner aspect of the uterus showed diffuse superficial hemorrhagic necrosis, the cavity containing masses of purplish-red coagulum. No definite evidence of fetal components could be identified grossly.

The other organs showed nonspecific changes, principally hyperemia. There was no evidence of exsanguination.

On microscopical examination of the uterus the disorganized remnants of a decidual reaction could be identified. In the decidua and in the poorly staining superficial myometrium there was focal and confluent hemorrhagic extravasation. The sinusoids were dilated, and in and about them were a few inflammatory cells, chiefly polymorphonuclear. In the cervical epithelium there was focal and confluent erosion.

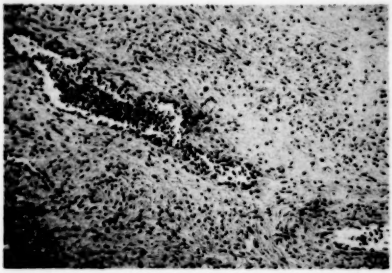

Figure 1. *Exudative Reaction in a Dilated Vessel of a Superficial Section of the Cervix. (Hematoxylin and Eosin Stain x 200.)*

The superficial cervical stroma contained foci of hemorrhage. There was a marked perivascular and intraluminal (Fig. 1) accumulation of exudative cells, mostly polymorphonuclear leukocytes, in the vessels in this location. This irritative reaction was much more prominent than it was in comparable areas in the uterus. Although the kidneys grossly were not regarded as showing significant changes, microscopical examination revealed the presence of numerous pigmented casts, chiefly in the lumen of the tubules designated as "lower nephron" (Fig. 2). The vasi recti were engorged. There was no significant alteration of the tubular epithelium. None of the other viscera showed changes of note except for hyperemia and moderately severe pulmonary edema.

Figure 2. *Pigment Casts in Lower Portions of the Nephron. (P.T.A.H. Stain x 50.)*

*A saturated solution of potassium permanganate contains 6.38 gm. per 100 cc. at 20°C. How much, if any, of the undissolved permanganate was carried along in the process of injecting the solution could not be determined.

For spectrographic examination for manganese* a specimen of heart blood and about half the uterus were submitted. Samples of these were separately ashed at low temperatures, and the resulting ashes were separately examined on the spectrograph. Manganese was detected in both the specimens, but the spectral lines of manganese from the uterus sample were more intense than those from the blood. A control specimen of normal blood showed very faint lines of the manganese spectrum, evidently representing the small trace of manganese normally present in this material.

The heart blood was fluid and dark purple. On exposure to air it turned to what appeared to be the usual normal red. Upon centrifuging, however, the serum was medium brown. The intensity of the color was far in excess of that which could possibly be accounted for by the presence of manganese dioxide alone. It was decided, therefore, to investigate this pigment further. With a visual (Zeiss) spectroscope, the serum specimen showed two absorption bands of about the same width, — but without sharp margins, — at 540 and 575 millimicrons. These observations were regarded as indicative of the presence of either oxyhemoglobin or alkaline methemoglobin, more likely the latter. The addition of strong sodium hydroxide and a crystal of sodium hydrosulfite (lykopon) produced characteristic bands at 535 and 560 millimicrons of hemochromogen — indicating that the pigment was a hemoglobin derivative. To establish definitely the nature of this pigment the following experiments were carried out:

In Vitro Experiments

To 10 cc. of heparinized normal whole human blood, 0.2 cc. of 1.0 per cent potassium permanganate was added. After centrifugalization, the plasma showed a deep brown color, and on comparison with an untreated specimen of the same blood, the hematocrit value was reduced from 44 to 35 per cent, indicating a hemolysis of approximately 20 per cent.

To normal human blood diluted and laked with distilled water, a drop of dilute potassium permanganate was added. This instantaneously converted the oxyhemoglobin to a brownish-red pigment, showing absorption bands at 540 and 575 millimicrons, *similar in all respects to those observed in the serum of the decedent.* Moreover, in a concentrated solution, a faint but definite absorption band was seen at 630 millimicrons. Upon reduction with crystalline sodium hydrosulfite (lykopon), this pigment was converted to reduced hemoglobin. These observations were explicable only if the brownish-red pigment were alkaline methemoglobin with merely a trace of the "neutral" form. Since methemoglobin in aqueous solution behaves as an indicator, both forms (neutral and alkaline) are present in varying proportions at pH values between 5 and 10. That the pigment was *not* hematin was shown by its reduction to reduced hemoglobin rather than to hemochromogen.

In Vivo Experiments

Rabbits were injected via the ear veins with a 1 per cent solution of potassium permanganate in amounts ranging from 1 to 5 cc. Immediately after injection the ear veins were outlined by a brownish discoloration, and in the animals allowed to survive, these veins became thrombosed and ischemic necrosis resulted. After injection there was an initial short period of minor collapse, but with this exception the clinical course of these animals was uneventful. In 2 animals killed at the end of 1 and 2 weeks there was no evidence of pathologic change. The kidneys of animals killed 24 hours after injection, however, showed pigment casts in the lumens of many tubules.

Serum was obtained from animals killed at periods ranging from 30 minutes to 2 days after injection. In all cases, alkaline methemoglobin was the principal abnormal pigment present. Continuous transmission curves made in the spectral region between 400 and 700 millimicrons showed the presence of alkaline methemoglobin, with only a trace of methemoglobin in "neutral" form. These curves are demonstrated in Figure 3. The steep rise of the transmission curves as they approach the longer wave lengths and the bands at 540 and 575 millimicrons are produced by alkaline methemoglobin. However, the slight "plateau" at 630 millimicrons is caused by the neutral form of the pigment. Although the pH of the serum in all cases was considerably below 8.0, spectrophotometric quantitation showed over 90 per cent of the pigment to be in the alkaline form. At present no explanation of this observation can be offered.

*Performed by Lieutenant Joseph T. Walker, Ph.D., State Police Chemical Laboratory, Massachusetts Department of Public Safety.

Discussion

Potassium permanganate is a strong oxidizing agent reacting promptly with protoplasm and most organic material, and at the same time undergoing reduction to the brown, almost completely insoluble oxides of manganese. Brown staining of tissues due to the formation of this oxide at sites of reaction may be regarded as pathognomonic of the injury produced by permanganate. Since the interreaction of the chemical and tissue is so prompt, the local necrotizing effect of permanganate is initially confined superficially to the site of surface contact. Further corrosive injury due to the formation of potassium hydroxide may take place, however, assuming that the reaction given below is a representative one:

$$4KMnO_4 + 2H_2O \rightarrow 4KOH + 2Mn_2O_7$$
$$2Mn_2O_7 \rightarrow 4MnO_2 + 3O_2$$

A characteristic of a strong alkali is to penetrate into deeper tissues, leading to progressive injury. Death in the case reported above probably occurred too soon for significant manifestations of potassium hydroxide penetration to take place. Two fatal cases of permanganate poisoning cited in the literature, however, may demonstrate the occurrence of deep-seated damage by secondarily formed potassium hydroxide. In 1 case[16] death occurred several days after permanganate ingestion from erosion of a gastric vessel and subsequent fatal acute hemorrhage. In the other,[17] after intra-urethral instillation of 200 cc. of 10 per cent potassium permanganate solution, perforation of the urinary bladder occurred and finally death from peritonitis. In some of the nonfatal cases described by McDonough,[15] scar-tissue deformation of vagina and cervix occurring as late complications are more easily explained by the deep-seated injury due to potassium hydroxide than they are by the more superficial injury caused by the permanganate molecule per se.

After ingestion, the clinical features of permanganate poisoning are those of local corrosive injury. The occurrence of secondary shock when sufficiently large amounts are taken (lethal dose 10 to 20 gm.)[18] has usually been regarded as a nonspecific general manifestation of the severe local injury rather than as systemic toxicity of permanganate per se. By the same rationale, no different interpretation is needed to explain collapse following permanganate injury of the reproductive canal.

A critical appraisal of the case presented indicates that, in contradistinction to the conventional opinion, permanganate may act as a systemic poison. Spectrographic examination of heart blood revealed the presence of a manganese compound, suggesting that absorption had taken place. Although the spectrographic examination did not

reveal the form in which manganese was distributed systemically, it seems highly probable that the compound present in the tissues post mortem was a reduction product of permanganate. This does not necessarily imply that the permanganate molecule as such did not enter the blood vessels during life. Certainly, the local environment was favorable for permanganate to enter the uterine circulation through the widely dilated sinusoidal channels of the richly vascular decidual tissue. Since potassium permanganate acts so quickly, hemolysis may have taken place in the small uterine sinusoids before this blood moved on into the venous circulation.

Apparently, it has not been generally appreciated that permanganate may act as an acute hemolytic agent, although the hemolytic effect of a somewhat similar oxidizing agent, potassium chlorate, is well known. Homma[19] states that permanganate causes methemoglobin formation in vitro but not in vivo. Palmieri,[20] in a fatal case caused by the suicidal ingestion of about 25 gm. of potassium permanganate, could not demonstrate methemoglobin in the post-mortem blood.* However, photomicrographs of the kidney of this case showed pigment in the lumen of collecting tubules resembling that seen in the case reported above. Concerning the presence of pigment casts in the kidney, it is probable that our patient would have developed the syndrome of lower-nephron nephrosis had she lived sufficiently long.

The formation of abnormal blood pigments in vivo can be brought about in a number of ways, but the particular hemoglobin derivative produced depends on mechanisms not yet well understood. Many chemicals, particularly the aromatic amino and nitro compounds, have the capacity of converting intracellular hemoglobin to methemoglobin without necessarily causing hemolysis. The spectrum of such a blood laked with distilled water in vitro shows methemoglobin, chiefly in the "neutral" form. On the other hand, intravascular hemolysis may or may not cause the formation of methemoglobin. As examples, a patient recently seen with blackwater fever showed a large amount of "neutral" methemoglobin in the serum, whereas in 12 cases of intravascular hemolysis due to the entrance of water into the circulation, not one showed evidence of methemoglobin in the serum; instead, the serum pigments consisted of oxyhemoglobin, alkaline hematin and bilirubin in varying proportions.[21]

The production of methemoglobin by permanganate, however, differs from the foregoing in that both hemolysis and pigment formation are caused by a strong oxidizing agent. With rupture of the red cell, the hemoglobin is freed and is instantly oxidized to methemoglobin. But since the amounts of permanganate used in the animal experiments increased the serum pH to only a slight extent (maximum, 7.65), it is difficult to see just why such a large proportion of the methemoglobin thus formed was in the alkaline form.

In addition to intravascular hemolysis, other types of systemic intoxication potentially may occur in acute permanganate poisoning. The first of these is hyperpotassemia. An increase in plasma potassium may have occurred in two ways in our case:

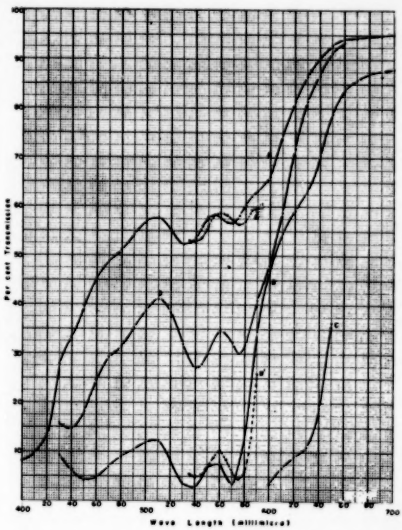

FIGURE 3. *Spectrophotometric Transmission Curves.*
A, B *and* C *represent serum from a rabbit injected intravenously with* 5.0 *cc. of* 1.0 *per cent potassium permanganate and killed half an hour later, diluted respectively* 1:21 *with* 0.1 *per cent sodium carbonate,* 1:5 *with water, and undiluted (wave-band width,* 14.0 *millimicrons).* A' *and* B' *demonstrate corresponding curves with a wave-band width of* 4.5 *millimicrons.* D *shows pure methemoglobin,* 72.5 *mg. per* 100 *cc., at a pH of* 10.7.

by absorption of potassium ions after breakdown of the permanganate molecule in the reproductive canal; and by the release of potassium incident to intravascular hemolysis. Although it is entirely possible that hyperpotassemia contributed to death, we have no objective chemical or other evidence of this. Potassium determinations in post-mortem plasma are unreliable in predicting the antemortem level because of the progressive increase in the potassium ion taking place after death.[22]

A second possible cause of systemic poisoning is the reduction product, manganese dioxide. Local absorption of this substance is highly limited because of its insolubility. Parenteral administration

*This author demonstrated sulfhemoglobin, which is often present in blood after death.

leads to convulsive seizures and terminal coma in animals[23] — symptoms that did not appear in the fatal case described above.

Summary

A case of a twenty-one-year-old pregnant woman who died approximately twelve hours after a potassium permanganate douche used as an abortifacient is presented. So far as can be ascertained, no similar case has been described.

The principal morphologic findings were extensive superficial hemorrhagic necrosis of the uterus, pigmented casts in the collecting tubules of the kidney, and evidence of acute intravascular hemolysis. The blood serum contained alkaline methemoglobin. The skin was discolored brown because of the presence of this pigment in the peripheral vascular bed.

On the basis of this case and of the experimental work reported herein, it is postulated that in acute permanganate poisoning death may be caused by one or any combination of the following processes: circulatory collapse (secondary shock) incident to severe local injury; intravascular hemolysis; hyperpotassemia due to local absorption of potassium ions; and potassium ion release incident to acute hemolysis.

Potassium permanganate in vivo and in vitro leads to lysis of red blood cells and to spontaneous conversion of released hemoglobin to methemoglobin, chiefly in the alkaline form.

Since the above report was written, another almost identical case has come under investigation in which an ante-mortem catheter specimen of urine was deep brown. The pigment showed the spectroscopic characteristics of methemoglobin; it was converted by sodium hydrosulfite to reduced hemoglobin, and then by a strong solution of sodium hydroxide to hemochromogen. This methemoglobin was chiefly in the alkaline form, and spectrophotometric quantitation showed total pigment concentration to be 16.7 gm. per 100 cc.

The post-mortem blood was likewise deep brown and showed only about 10 per cent of red cells after centrifuging, and the plasma had the same appearance and gave the same reactions as the urine. Quantitated as alkaline methemoglobin, the plasma concentration was 14.9 gm. per 100 cc. Since post-mortem blood samples frequently show high concentrations of red cells, this figure (indicating almost complete hemolysis) is not so unreasonable as it seems at first sight. Evidently hemolysis and oxidation of hemoglobin to methemoglobin continued after death.

Although it was impossible in this case to obtain information about the chemical used in the douche, potassium permanganate was doubtless employed since the spectrographic examination of uterine tissue showed definitely a larger amount of manganese than normal.

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CLINICAL NOTE

HEREDITARY MULTIPLE EXOSTOSES

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HEREDITARY multiple exostoses are a distinct clinical entity more frequently encountered than is generally appreciated.

We have recently had the opportunity of studying 4 members of a Negro family who had the condition. Few cases occurring in Negroes are reported in the American literature.[1-3] To our knowledge this is the first Negro family studied and reported.

The cases were typical in both the clinical and roentgenologic aspects, varying, of course, in degree. It was our intention originally to include total protein, dextrose tolerance, calcium, phosphorus and other hormonal excretion studies in the investigation. Owing to circumstances beyond our control it was not possible to do so.

CASE REPORT

CASE 1. M. C., a 40-year-old Negress, the mother of the family, demonstrated completely asymptomatic growths about the knees with genus valgus. She was unaware of them up to the time x-ray films were taken. Consanguinity was denied and no further genealogy could be elicited. The creatinine excretion was 0.96 gm., and the 17-ketosteroid excretion was 3.9 mg.‡ Both values were low, but their significance, if any, is unknown.

CASE 2. A. C., a 19-year-old daughter, first noticed the growths about the knees when 9 years old. There was involvement of the extremities, and full extension of the forearms was not possible. The tumors progressed in size until the age of 13, after which they remained quiescent. She had some aching in the feet and ankles for a week or more after even trivial trauma, but otherwise was completely asymptomatic. A urinalysis, hemogram and blood sugar, alkaline phosphatase, serum calcium and phosphorus determinations were normal. We were unable to obtain total 24-hour urine specimens.

CASE 3. In S. C., a 14-year-old son, the exostoses first appeared at the age of 6 and had continued to increase in size. There was shortening of the forearms, with lack of full extension, as well as some limitation in movement of the legs. The laboratory procedures enumerated above gave normal values.

CASE 4. In S. C., a 9-year-old daughter, the protuberances were noted within the past year with seemingly no progression. There were no symptoms.

DISCUSSION

As Ehrenfried[4] stated, the disease is a distinct clinical entity with the following characteristics: the occurrence of multiple, more or less symmetric cartilaginous and osteocartilaginous overgrowths within and on the skeletal system; the presence of certain typical distortions and deformities of the skeleton; and the demonstration of inheritance in a large proportion of the cases. The appearance of the knees of the members of the family under discussion is shown in Figure 1.

The hereditary nature of the condition was most extensively studied by Stocks and Barrington,[5] who reported that out of a total of 1189 cases a definite familial history was elicited in 76.5 per cent; 69.6 per cent of the patients were males. The disease probably cannot be transmitted through an unaffected male but can definitely be transmitted through an unaffected female, and the suppression or latency of the disease in one generation does not involve any weakening in the power to transmit it to the next generation. The association of multiple exostoses with multiple enchondromas is more frequent in patients with a hereditary history.

FIGURE 1. *Photograph of the Family at First Examination.*

Congenital exostoses and a case discovered shortly after birth have been described,[6] but, by and large, the condition is mostly frequently detected during the periods of growth up to puberty, and few cases are reported in which the tumors appeared after the age of twenty.

There may be no signs or symptoms so that the condition is detected only on x-ray study, usually for some unrelated condition. In other cases the growths may be visible and palpable but cause no other complaints. In typical cases there are certain characteristics: shortness of stature due to defective growth of the lower extremities whereas the trunk is normal; forearm deformities, including shortening, bending and inability to extend the forearms fully (asymmetry of the extremities may be obvious); and genu valgum (scoliosis, kyphosis and

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‡The determinations were made in Dr. Lawrence Kyle's laboratory at Georgetown University Hospital.

talipes valgus occur, but there is no alteration in the physiognomy).

The patient may have complaints referable to joint interference or pressure phenomena on nerves or blood vessels, or the new growths may cause pain. Growths in the pelvis are a cause of dystocia.

The condition is primarily limited to the long bones, where the tumors may appear anywhere along the bone but are more frequent at the juxta-epiphyseal regions. Furthermore, it has been shown

FIGURE 2. *Typical Roentgenologic Appearance of the Involved Bones.*

that the most actively growing end of the bone bears the brunt of the involvement. The growing ends of the lower-extremity bones are nearest the knee, whereas in the upper extremity they are located at the shoulder and wrist, which explains the frequency of osteochondromas around the knee and their comparative rarity near the elbows.

The characteristic roentgenologic picture is that of numerous osteochondromas in the metaphyseal region of the long bones (Fig. 2). The metaphysis is wider and somewhat longer than normal, and the cortex is thin. The exostoses vary in configuration, usually point in the direction of muscle pull and may arise from a broad base of cancellous bone or from a pedicle. There may be associated enchondromas. The ends of the bones may fail to develop, giving the femur a squared-off shape. When this happens in the radius and tibia there is bowing of the adjacent bone — namely, the ulna and fibula. Synostoses of the upper end of the fibula with the tibia and fusion of the lower end of the ulna with the radius can occur. The Madelung deformity of the radius may be present.

Grossly, the exostoses are firm, lobulated tumors covered by a glistening, fibrous envelope that, on cutting, reveals a thin outermost layer of connective tissue beneath which, and appearing more prominently, is a zone of cartilage. The innermost regions are occupied by bone. Microscopically the surface envelope is seen to be composed of fibrous connective tissue, which in places blends almost imperceptibly with bone, whereas elsewhere it joins the subadjacent cartilage. The cartilage in its deeper layer becomes calcified and may either abut on spicules of laminated bone or merge into a region of cartilage removal and bone deposition. In the latter areas osteoblasts and osteoclasts may be seen. The bone is cancellous in structure, and the interspaces are occupied by fatty marrow.

Malignant degeneration is rare, being more common in cases of the single than of the multiple type.[6,7] If neoplastic changes arise in the multiple cases they will do so from one growth so that an increase in size in a previously dormant osteochondroma should alert one to the possibility. Osteogenic sarcoma, chondrosarcoma, chondromyosarcoma and spindle-cell sarcoma are the malignant lesions that have been described. Osteogenic sarcoma arising from an exostosis is less malignant and bears a better prognosis than that of the primary type.

Many theories[7–14] have been put forth in an attempt to explain the etiology. The fundamental cell in exostoses of enchondral or intramembranous origin, as well as enchondromas, is the mesenchymal cell. This cell, depending on the stage of its differentiation when stimulated as well as the duration of stimulation, can give rise to connective tissue, cartilage or bone. The stimuli that may initiate the progress are as follows: hereditary diathesis and defect in bone growth itself; growth, with its concomitant stresses and strains; metaplasia due to alteration in the physicochemical environment induced by hormonal or other metabolic factors; and trauma or infection in certain cases of single growth.

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A COMPARISON OF PTEROYLGLUTAMIC ACID AND LIVER EXTRACT MAINTENANCE THERAPY IN SPRUE*

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THE effects of synthetic folic acid in sprue have been studied by several groups of investigators. Both Darby et al.[1] and Suarez and his associates[2] reported that the substance had a prompt and dramatic clinical and hematologic effect with remissions comparable or superior to that which follows liver therapy. A daily dose of 2.5 to 5 mg. was considered to be adequate although in many cases the periods of observation were brief. Davidson and his co-workers,[3] on the other hand, treated 10 cases of sprue with folic acid with only moderately good hematologic results, noting that macrocytosis persisted.

The present report deals with hematologic and certain clinical changes observed in 7 patients with sprue receiving maintenance dosage of synthetic folic acid for a period of at least one year. All these patients had chronic disability in spite of years of nutritional therapy, liver and vitamin supplements. This report deals with an appraisal of the comparative effects of liver and folic acid as maintenance therapy in such cases. Results of fat-balance tests and roentgenographic and biochemical studies are being presented elsewhere.

All patients were white adults native to the Carolinas, and had been under observation at this hospital for a number of years. A report on many of them has appeared in the study made by Hanes.[4] Careful and continued follow-up observations on this group ranged from four to eighteen years, during which time they were hospitalized for treatment of sprue. All had symptoms and signs typical of the sprue syndrome: recurrent diarrhea, steatorrhea, meteorism, progressive loss of weight, glossitis, anemia and abnormal x-ray patterns of the small intestine. Two to four hospital admissions had been required because of recurrent relapses during the preliminary time of study. The patients had all returned to the clinic at intervals of three months or less, because of a variety of complaints and disabilities.

Seven patients, 4 of whom were males and 3 females, with chronic sprue were chosen for study. Before the beginning of folic acid therapy, all of them had received prolonged treatment with low-fat diets, various vitamin preparations, and purified liver extract, dosage of 30 units to 60 units, administered parenterally once a week. These measures had failed to restore to normal the weight, stools and blood values.

Two of the patients included in this report were not having diarrhea and had not taken parenteral liver for several months. They were given folic acid because they were underweight, had abdominal distention and lacked a sense of well-being. That folic acid is beneficial in such cases can be noted in Cases 2 and 3 (Table 1).

For more than a year, these 7 patients have been closely observed while receiving synthetic folic acid‡ orally as the sole specific therapeutic agent. All were rehospitalized for complete fat-metabolism studies and were examined in the clinic once a month. The dosages as well as the hematologic and clinical findings before and after treatment with folic acid are given in Table 1 and 2. The values for the white-cell count and differential formula and reticulocyte percentage were within normal limits in these cases and therefore are not included.

Discussion

Hematologic Features

Table 2 shows the blood values before the start of folic acid therapy compared to the values one

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year later. Severe anemia was not a feature in any of the cases of this group. The blood picture in the majority was macrocytic, as judged by the stained films and the elevated mean corpuscular volume. In a patient who had at one time had a macrocytic anemia a hypochromic anemia developed. In our experience, which confirms that of others,[5] the anemia associated with the sprue syndrome in many cases is resistant to all forms of treatment. Strictly normal blood values have not been obtained despite the use of both purified and crude liver extract, iron and vitamins.

The effect of folic acid in maintaining blood values in patients who had received the conventional sprue therapy is shown in Table 2. Here it is noted that the hemoglobin, red-cell count and hematocrit were lower in Cases 5, 6 and 7 after a year of folic acid. In Case 7, despite a daily dosage of 60 mg., folic acid proved a complete failure. The patient steadily lost weight, her appetite declined, steatorrhea and diarrhea continued, she developed glossitis, and her state of relapse was so severe that she was hospitalized. She was found to have multiple absorptive deficiencies. These included hypoproteinemia associated with edema, hypocalcemia accompanied by tetany, a flat glucose tolerance curve, subnormal levels of blood potassium and very low levels of plasma vitamin A, which did not rise after the administration of a large test dose of the vitamin. Not only was she refractory to folic acid but also purified preparations of parenteral liver in large doses proved ineffective. Only after the frequent administration of massive doses of crude liver extract, "intraheptol," given intravenously were we able to induce a remission.

TABLE 1. *Clinical Effects of Folic Acid in Chronic Sprue.*

CASE NO.	PERIOD OF TREATMENT	NO. OF STOOLS DAILY	CHARACTER OF STOOLS	TONGUE CHANGES	WEIGHT	APPETITE	ABDOMINAL DISTENTION	SENSE OF WELL-BEING
					lb.			
1	Before folic acid	2–3	Liquid, frothy	0	152	Good	+	Fair
	After folic acid	1–2	Soft-formed	0	152	Good	0	Improved
2	Before folic acid	1	Normal	0	101	Fair	0	Fair
	After folic acid	1	Normal	0	110	Good	0	Improved
3	Before folic acid	1–2	Soft, bulky	0	97	Poor	+	Fair
	After folic acid	1	Normal	0	104	Good	0	Improved
4	Before folic acid	4–5	Watery, frothy	+	128	Poor	+	Poor
	After folic acid	1	Formed	0	141	Good	0	Improved
5	Before folic acid	3–4	Liquid, bulky	+	128	Poor	+	Poor
	After folic acid	1–2	Soft-formed	0	129	Fair	+	Improved
6	Before folic acid	2–3	Bulky, watery	0	108	Fair	+	Fair
	After folic acid	1–2	Soft, foul	0	112	Improved	0	Improved
7	Before folic acid	7–9	Liquid, bulky	0	99	Fair	+	Poor
	After folic acid	7–9	Unchanged	+	67	Worse	+	Worse

Clinical Effects

In Table 1 the clinical changes as well as the dosage of folic acid employed are listed. All patients received the same preparation of folic acid in tablets orally. Contrary to reports by certain other investigators that doses as low as 5 mg. daily suffice for most cases, that amount was totally inadequate in our cases. On such small doses, the patients exhibited only a fraction of the degree of improvement seen after an increase to 30 mg. daily.

TABLE 2. *Blood Values before and after Folic Acid.*

CASE NO.	PERIOD OF TREATMENT	HEMOGLOBIN	RED-CELL COUNT	HEMATOCRIT	MEAN CORPUSCULAR VOLUME	THERAPY
		gm./100 cc.	*×10⁶*	*%*	*cu. microns*	
1	Before folic acid	13.5	4.40	44	100	15 units of liver extract intramuscularly each week
1	After folic acid	14.2	4.50	44	98	30 mg. of folic acid daily
2	Before folic acid	15.0	5.00	47	92	None
2	After folic acid	13.6	4.55	44	96	15 mg. of folic acid daily
3	Before folic acid	15.0	4.64	44	94	None
3	After folic acid	13.0	4.60	42	91	30 mg. of folic acid daily
4	Before folic acid	13.1	3.82	44	112	None
4	After folic acid	13.5	4.45	42	94	30 mg. of folic acid daily
5	Before folic acid	13.0	4.86	39	81	45 units of liver extract intramuscularly each week
5	After folic acid	11.5	4.00	36	90	30 mg. of folic acid daily
6	Before folic acid	13.5	4.35	42	97	30 units of liver extract intramuscularly each week
6	After folic acid	12.2	4.00	36	90	30 mg. of folic acid daily
7	Before folic acid	9.3	5.00	34	70	15 units of liver extract intramuscularly each day
7*	After folic acid	10.0	3.45	30	87	60 mg. of folic acid daily

*This patient subsequently responded to crude liver extract administered intravenously.

A progressive gain in weight was enjoyed by 4 patients; 2 showed no essential weight change, and 1 (Case 7) had a marked drop in weight. All but 1 admitted to an improvement in appetite and sense of well-being. Glossitis disappeared within a week. Diarrhea, a persistent complaint in 4 patients, was much better controlled by folic acid than by liver. Within two weeks of starting folic acid, the patients exclaimed upon the decrease in number as well as bulk of stools. Those who had suffered diarrhea at night as well as in the daytime were improved until they could sleep without interruption. Diarrhea ceased completely in 1 severe case. The other patients began to enjoy periods of normal bowel habits alternating with periodic recurrences of diarrhea. Such recurrences were at long intervals and were preceded by ingestion of foods high in fat. The relief of abdominal distention was pronounced in the majority. All patients but 1 were enabled to perform normal work and earn a living. No neurologic disease or evidence of any harmful effect from the folic acid administration was seen. With the exception of Case 7, there were no relapses.

Regarding the chronicity of sprue, it has been our experience that about half the patients go into remission after initial treatment, and remain well for many years. On the other hand, there are a number of patients, like those in this report, whose histories of sprue extend back for several years and who have suffered various degrees of disability. These patients have been difficult to control. They have required close supervision of diet and specific therapy. Prior to the assay of folic acid in this group, purified liver extract given parenterally had been relied upon fairly satisfactorily as the chief mode of control. Injections of 30 to 60 units were given once to three times each week. Exacerbations occurred in the women during pregnancy despite maintenance liver therapy, and relapses were suffered by the men when an attempt to prolong the interval between injections of liver was made.

Folic acid, by comparison with liver extract, has proved to be of equal value, and perhaps superior in some cases, in the treatment of 6 of the 7 patients of this group. These patients followed essentially the same dietary regime while receiving folic acid as when taking liver extract. They were not given supplemental vitamins, since, in our experience, these have proved worthless. Neither folic acid nor liver extract alone can be expected to be a cure-all in sprue. Folic acid can be given orally. This is a great convenience to the patient. Also, most of them dislike injection therapy.

By definition, the term sprue as used here designates the sprue syndrome as described by Hanes,[4] and there seem to be no cogent reasons for attempting to differentiate the tropical and nontropical forms.

Summary

Observations on the effects of folic acid given for at least a year to a group of sprue patients are presented. Folic acid has a beneficial effect in general, but does not produce complete remission in all types of cases. The majority of patients gained weight and had less diarrhea. One patient relapsed, with the development of weight loss, diarrhea and glossitis while receiving 60 mg. daily. This case, however, was also refractory to purified preparations of liver extract and responded only to crude liver extract given intravenously.

Blood values were not quite so well maintained by folic acid as by liver extract, an experience encountered in a number of cases of pernicious anemia so treated. Three of the patients in whom folic acid was substituted for liver extract showed a drop in blood values over a period of a year. Despite this fact, they all experienced definite clinical benefits that had not been enjoyed while they had been on liver therapy.

The dosage requirements of folic acid varied from one patient to another. Whereas 15 mg. daily sufficed for some, it was observed that increasing this dosage to 30 mg. in other cases was followed by gain in weight and considerable relief of gastrointestinal symptoms.

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MEDICAL PROGRESS

PHYSIOLOGY OF HUMAN CONCEPTION*

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ALTHOUGH simple parthenogenesis is not at all uncommon in invertebrates — for instance, in ants and bees — it does not, as far as is known, occur in human beings, who must produce eggs and sperm and then effect their conjugation. The following discussion concerns itself only with the somatic aspects of this complicated process since the beguiling psychologic motivation and mechanisms lie in a mixture of too much fancy with too little fact.

Among various vertebrate species the sequential evolvement of the primordial oocyte, within its epithelial capsule, to the mature ovum, in the rupturing follicle, is impressively similar, although the duration of the successive phases may be very different. We are thus led to believe that, in human beings, factors identical with those recognized in laboratory animals are involved in the growth process. There is no specificity of pure hormones, for those from one animal are effective in others. The degree of their potency and the susceptibility of the target organs, however, vary widely among species. Of the gonadotropic hormones found effective in animals some are known to be produced likewise in human beings, and others are reasonably assumed to be. Doubtless their effects in human beings are the same, in kind, if not in degree.

In the human ovary at puberty there are said to be, distributed through the stroma, more than 10,000 ova in various stages of development.[1] Some are small oocytes surrounded by a single layer of epithelial cells. These nurse cells, the precursors of the granulosa, and the central oocyte are believed to be derived from the mesothelium that covers the original formative gonad. This mesothelial derivative becomes the germinal epithelium Whether in human beings all primitive ova are present at birth or new ones, from time to time, descend from the germinal layer into the cortex is not known. Hartman[2] has shown that oogenesis continues in the rabbit, and Allen[3] that this is so in the mouse, and Mossman[4] states that it occurs in the pocket-gopher. Although Hertig[5] has not incidentally seen mitotic activity in the germinal layer of any mature ovary it seems at least possible that production occurs, albeit infrequently, in adult life.

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MATURATION OF THE FOLLICLE

Hisaw[6] has recently reviewed pertinent follicular biology in animals and from his discussion one may plausibly theorize on this process in patients and, complacently ignoring the absence of many proofs, describe it as follows. Governed by a "self-contained system of organizers," the primordial oocyte while attaining full size, effects an investment of several layers of granulosa cells from the primitive epithelium surrounding it. This simple group of ovum and nurse cells causes the adjacent connective tissue to develop the theca interna. This, then, consists of a specially vascularized tissue of enlarged cells, which sooner or later, and again, automatically, by reason of their own intrinsic enzyme system, secrete estrogen.

The estrogen from the theca interna now empowers the granulosal layer to produce a fluid that it holds within a small, newly formed antrum. The appearance of this small vesicle terminates Hisaw's first stage, and ushers in the second stage of follicular development.

Estrogen thus appears as the indispensable self-organizer of the graafian unit. After responding to estrogen the follicle "gains competence" to react to the follicle-stimulating hormone of the hypophysis (FSH). This requirement of preliminary conditioning by estrogen explains why some follicles mature and others do not, for it is FSH that stimulates gross enlargement of the vesicle, but only after estrogen has first primed the granulosa and possibly its source, the theca itself. Estrogen also has other targets. It induces the hypophysis gradually to quit production of FSH and to secrete luteinizing hormone (LH). It is now apparent that both LH and the previously secreted FSH act on the theca to start the luteinizing process.

With the well developed follicle, about 1 cm. in diameter, Hisaw's third stage begins. As this progresses, more estrogen, together with gradually increasing amounts of progesterone is secreted by the theca, and the follicle extends its growth toward maturity. It enlarges to a diameter of even 2 cm. by the accumulation of fluid; the increasing estrogen reacts on the hypophysis to diminish its production of FSH and to bring forth more LH. As these combined gonadotropins act on the follicle most sensitized by estrogen and previous FSH, this one secretes more progesterone. Furthermore, it

acquires reactivity to what is a variant of LH or is a new pituitary gonadotropin, luteotropin. Hisaw's fourth stage of development, that of the corpus luteum, begins.

Meanwhile the ovum has matured and, in its first miotic division, has split its chromosomes longitudinally and extruded half their substance in a polar body. The follicle ruptures, floating out the mature ovum on the liquor folliculi (described below). With rupture the luteinization that started the third stage of follicular maturation continues. More progesterone, as well as estrogen, is secreted. As estrogen continues to suppress FSH production by the anterior pituitary body, LH and its successor, the luteotropic hormone, acquire ascendancy and establish the corpus luteum. For about ten days this produces gradually increasing amounts of estrogen and of progesterone. After the first week it starts morphologic regression, for it loses susceptibility to further stimulation by pituitary gonadotropins. Only chorionic hormone, secreted by the trophoblast of the differentiated conceptus, can revive this declining gland.

Meanwhile, what has happened to the several other graafian follicles that by estrogen had been sensitized to FSH and had begun to grow? They reached that degree of maturity at which they were ready to start luteinization — Hisaw's third stage of development. They failed to qualify at this point because of a delicate species quality. In the human subject there seems to be just enough LH in co-operation with FSH to evoke effective amounts of progesterone and increased estrogen in only the most receptive follicle. This most sensitive follicle takes all there is, and its resultant endocrine activity diminishes the hypophyseal product below the reactive threshold of the other follicles or progesterone desensitizes them to the FSH and LH present. It is known that these other thecated follicles regress, leaving only those with well developed antra but without well luteinized thecae internae.

Thus it is in human beings that, typically, only one follicle ruptures; other competing follicles regress. Time is required after the corpus luteum involutes for more follicles, by their own estrogen, to become successively responsive to FSH and to LH that gradually increase when the regressing corpus luteum diminishes its production of estrogen and progesterone, which respectively had inhibited the very hypophyseal activity that evoked each of them.

Ovulation

The accumulation of liquor folliculi within the distended granulosa and theca of the maturing follicle may increase the internal pressure. Were this so, something must give or the granulosa and the ovum would be crushed. Perhaps the pressure is transmitted through the concentric musculated laminations of the thecae interna and externa to the less organized stromal connective tissue, surrounding the follicle. This would then recede before the stress of the follicle and its supporting thecae. At all events, unless only superficial follicles mature, the whole growing graafian unit moves toward the surface. It bulges as the cortical germinal layer and the underlying thecal layers as well become thinner. Finally, the continuity of these surface layers is broken, and the fluid escapes. Floating out with it are the disrupted portions of the granulosa and cumulus. In the latter is the ovum within its zona radiata of more cohesive granulosa cells. Recently, Kraus[7] experimented with rabbit follicles in an attempt to determine the factors of rupture. From these experiments it was deduced that not internal pressure, local enzymatic action, muscular force in the theca or "pull" of the cilia of the fimbria was involved. It was therefore postulated with proper serenity that there occurred a "morphologic change in the stigma" of unknown nature and caused by unknown agents.

Time of Ovulation

As is common, with only rare exceptions, to all species of animals studied, a short individual life is the lot of human germ cells. To serve their function those of the two sexes must unite within a number of hours after being freed, the ovum from the ovary and the sperm from the male genital tract. The chance of conception in human beings is exceedingly slight, indeed perhaps impossible, if the nearest *preceding* coitus occurs more than forty-eight hours before ovulation, and the first *succeeding*, more than twelve hours after escape of the egg. Once miosis, the process of diminution of chromosomes, has begun, as it does usually in the follicle with the first polar division, it progresses steadily. When terminated in the tube, probably at most twenty-four hours later, more chromosomes, to complete the species number, must soon be added or life processes cease. Furthermore, it seems likely, from studies such as that of Blandau and Young[8] in the guinea pig and those of several others in different species, that if ova approaching decease do become activated, or if an aged sperm succeeds in fertilizing an ovum, the resultant conceptus is very likely to be defective. It is of great practical importance, therefore, to know just when in the menstrual cycle ovulation takes place.

The number of independent biologic factors involved in the whole process of ovulation from beginning luteinization of the theca interna to the final rupture of the mature follicle makes evident the probability that no sign of the exact moment of ovular release will ever be recognizable. Ovulation is the result of the interplay among hormonal agents such as carefully adjusted proportions of FSH and LH, physical agents such as accumulation of fluid in the follicle and migration of this enlarging cyst to the cortex, and possibly enzymatic agents or even the more obscure internal "cell organizers"

that cause final dissolution of continuity in the wall of the follicle and in its thinned-out cortical cap. It seems unlikely that all of these are trigger mechanisms, which function with exact time relations to each other. It is of great interest in this connection, on the other hand, that Sawyer, Markee and Hollinshead[9] have shown that the hypophysis in the rabbit responds to the coital stimulus within at most three minutes. It has long been known that, in rabbits, follicles rupture from ten to fourteen hours after coitus. But even in rabbits the exact time of ovulation is not easily detectable without inspection of the ovaries. An indicative change in electropotential was reported by Burr et al.[10] and Reboul, Friedgood and Davis,[11] but this is not a useful method even in rabbits, and Snodgrass[12] has shown it to be quite undependable in human beings.

In the monkey and the cow the approximate time of ovulation, within hours, may be determined by repeated palpation of the ovary through the rectum — a method not likely to be practical with patients. Except in rare cases "mittelschmerz" is quite unreliable. The specific cause of the pain is unknown, so that even in the occasional case in which it is so peculiar as to be unmistakable it can do no more than indicate the process of ovulation and not the actual event.

It is now generally admitted that ovulation occurs about two weeks before the manifest onset of normal menstruation. This must be so, for flow is precipitated by withdrawal of corpus luteum hormones, and the corpus luteum may be said to acquire definitive form and function within perhaps a day of ovulation, and to remain active for about two weeks. The duration of luteal dominance is deduced from observation of the effects of its specific product, progesterone, on the endometrium,[13] by detection in the urine of pregnanediol,[14] an excretion product of progesterone,[15] by proportional changes in urinary estrogens[16] and by cytologic and histochemical study of corpora lutea themselves.[17] Comparison of previllous human conceptuses with those of the macaque, in which the actual ovulation ages are known, because the actual day of ovulation had been determined by Hartman's method of bimanual rectal palpation, gives final confirmation to the deduction that human ovulation occurs *about* fourteen days before the first day of normal menstruation.[18]

Consideration of the inexactness of all these data is salutary. In the cytologic studies of the endometrium, in the biochemical assays of excretion products and in the cytologic and histochemical studies of corpora lutea, the results pointing to about fourteen days of function either were averages of findings or were postulated from a theoretical date of ovulation and then found to agree with this date within a statistically significant limit of error. The constancy of the agreement was hence taken to substantiate the theoretical date. In the case of the actual conceptuses whose ovulation ages could be determined fairly accurately, the time between the day of ovulation and the onset of menstruation had to be estimated, for, of course, in the particular pregnant cycle, there was no subsequent menstruation. The dates when catamenia would have occurred were arrived at by reference to each mother's previous menstrual cycles, which are generally constant within an inclusive range of 5 days.

In 1937 Rubenstein [19] revived interest in the fact that during most menstrual cycles the curve of daily basal temperatures is diphasic, lower in the first part of the cycle than in the second. He correlated the shift in temperature levels with changes in the vaginal smear that had been shown by Shorr and Papanicolaou[20] to be attributable to ovarian function. In 1944 Klaften showed,[21] by experiments with amenorrheic women, that the increase in temperature was a function of progesterone. Thus, it is now generally believed that when the temperature rises to stay it may be assumed that the corpus luteum is functioning and, so, that ovulation has occurred.

To minimize disturbing factors the temperatures recorded are best taken each day promptly on awakening and before any activity beyond placement of the thermometer. For those who are careful, mouth temperatures give informative curves, but for most women rectal or vaginal readings are more dependable. There is no uniformity in the curves of women in general, except that during the ovulatory cycles they are diphasic. Indeed, among succeeding ovulatory cycles in the individual woman, the temperature levels and the gradients may both be noticeably dissimilar. Examination of the completed curves, however, will usually reveal either the sudden or the gradual termination of the lower first phase. The day or days of the last lowest temperature from which, either abruptly or by stages, it rises to stay are generally taken to be the day or days of the ovulation phase. Only very rarely does one see a chart in which this apparent sign of ovulation is beyond the limits of 14 ± 4 days before the onset of flow. In most women this assumed ovulation phase is found to lie usually within the range of 14 ± 2 days before menstruation, but every woman is likely to stray out of range every now and then.

Tubal Function

Whence goes the 1, 2 or even 6 cc. of liquor with its indispensable egg when it escapes from the follicle? It must flow into the variable amount of peritoneal fluid that bathes all viscera. Doubtless it is not infrequently dispersed about the pelvis, washing the ovum to distant places beyond the reach of spermatozoa. To prevent this in some mammals there is an ovisac, surrounding the ovary, a delicate serosal receptacle attached to and open-

ing into the tube. Human beings have not thriftily acquired this little catchbasin that would prevent loss of eggs; they have a more complicated and defective mechanism.

The fimbriae of the tubes vary widely among women. Some consist of short and closely approximated growths of ciliated epithelium on a narrow, flat collar of musculated connective tissue surrounding the ostium. This collar may have a radius of less than 1 cm. Sometimes the flared end of the tube is found to have a long fringe that may extend outward to a radius of 2 cm. (especially on the abovarian margin). This fimbriated structure is important, and modification of the ideal wider collar may be very significant to fertility. Westman[22] has credibly postulated that as ovulation approaches, muscle fibers in the tubo-ovarian ligament contract to approximate the fimbria to the ovary and that, furthermore, other muscle fibers in the thin connective-tissue collar spread out this structure so as to engross the ovary in a curved, fan-shaped envelope, which constitutes a homologue of the ovisac of some so-called more primitive animals. Careful exposure of adnexa at laparotomy during the ovulatory phase often discloses both ovaries thus covered.

Improving this system of receptivity is the ciliated mucosa that forms the surfaces of this extension of the ostial border adjacent to the ovary. In functional position this epithelium faces the ovary, and the beating cilia establish a current from the ovary and the pelvic cavity toward the uterus. Physiologically, the liquor folliculi is pulled toward the tube. Carried in the liquor, the ovum in its tattered vestment of granulosa doubtless thus floats into the ampulla, when the system works. Otherwise, and perhaps more often than has been thought, the liquor is dissipated and the ovum lost in the pelvis.

The quality of tubal fluid with regard to the egg may be very important, but at the moment all one knows is that it offers a warm, moist medium in which the ovum may be fertilized and conveyed to the uterus. Mouse ova, removed from the tube and placed in the anterior chamber of the eye,[23, 24] have achieved implantation there. Rat ova, similarly obtained and properly placed, have implanted under the capsule of the kidney.[25] Once fertilized, neither apparently suffered by deprivation of tubal fluid.[26]

Judging by 4 activated human eggs cultured in vitro and 1 human incipient morula found in the uterus, there is little if any increase in protoplasmic bulk up to the 4-cell stage. Between this and the 8-cell stage the vitelline mass apparently does grow, but probably in human beings this growth occurs in the uterus. (The mouse eggs observed by Lewis and Wright,[26] as well as the rat eggs studied by Alden,[27] may have increased in size in the tube.)

It appears that tubal fluid may be not only a protective covering and vehicle for the egg but also a substrate delicately adjusted in pH and osmotic pressure for the fertilization process and, too, a nutrient medium for ova. The possibility that the ovum makes respiratory demands on this tubal product must be considered, but of this nothing is really known.

Sojourn in the tube is fairly short. A 4-cell human morula, possibly abnormal, but yet not more than four days old was found by Hertig[5] in the uterine cavity. Two other human conceptuses between seven and eight days of age, both doubtless normal, were found to be so well embedded in the endometrium as to indicate that nidation had been started not later than the sixth postovulatory day. There seems good reason to believe, then, that the antrum-containing blastocyst takes shape about the fifth day and that at this time the new organism must be where the rapidly differentiating trophoblast will be offered appropriate nidation. How does it get there?

The tube is roughly seven hundred times longer than the diameter of the inert egg (100 mm. versus 0.150 mm.). The comparatively long haul to make delivery in the uterus is accomplished by downward propulsion of the fluid carrier with its cargo by the ciliated endosalpinx, doubtless aided by the more effective peristalsis of the myosalpinx. During the few days of its journey the single cell, by mitotic division of the vitellus, changes into at least or at most a 4-cell morula. Some time after this cleavage the jel-like pellucida disappears. Fawcett[24] and Runner[23] have called attention to the fact that even for this process neither the tubal fluid nor the uterine fluid is necessary in the mouse and rat, for this structure is equally well disposed of in such foreign places as the eye, the kidney or the peritoneal cavity.

The tubes also serve the spermatozoa as conduits at least. How the motile organisms progress through them is considered below. Here it is pertinent to note that there is reason to suspect that, in the rabbit, tubal fluid supplies an enzyme system that conditions the sperm for facile entry into the vitellus through the vitelline membrane.[28] Such a possible biochemical process must be nicely integrated with the probable antigen system effecting conjugation so carefully studied by Loeb,[29] Tyler[30] and others, mentioned below under "Fertilization."

Uterine Function

As segmentation progresses, the conceptus increases in bulk: it takes something from the thin layer of fluid separating the anterior and posterior surfaces of the endometrium. This must include metabolites as well as water, but of their nature little is known beyond the fact that starting about four days after ovulation, or about the time the ovum reaches the fundus, the uterine glands disgorge a secretion containing glycogen. During the fifth day progressive cell division of the

blastocyst results in differentiation into two kinds of tissue. One forms the inner cell mass, which projects into the newly formed antrum. This will develop into the embryo proper. The other specialized group of cells is the outer trophoblast, which constitutes the wall of the antrum. The latter tissue apparently secretes some substance that causes vasodilatation and even extravasation of blood in the neighboring maternal tissue, which, normally, is the endometrium.[24] The outer, or syncytial, trophoblast at the embryonic pole also engorges the surface epithelium as it "forages" its way toward the vessels in the stromal bed underneath.[31] In the human being it goes farther. In the youngest implanted specimen, barely seven days old, one sees the syncytium phagocytizing stromal cells as well, while the whole organism is gradually enclosed within the endometrium. Judging from the effect of the trophoblast on several different tissues, — the iris,[23, 24] the kidney capsule,[25] the peritoneum, the endosalpinx and the endometrium, — access to maternal blood is the ultimate objective. While struggling on to this complete food, the trophoblast must be nourished by contributions from intercellular fluid and from the ingested stroma cells. The biochemicals, necessarily found here, have not been identified except for phosphatases, glycogen and some lipids.[32]

There seems little doubt that whatever the food material is, its presence is caused by progesterone and estrogen from the corpus luteum. It was stated above that the corpus luteum of the nonpregnant cycle ceases further growth after about the seventh day following ovulation, for then its ability to respond to pituitary gonadotropins has reached its peak. If conception has occurred, however, the sequence changes. Until the definitive placenta is formed — that is, until there is plenty of maternal blood available to fetal villi capable of utilizing it, — the trophoblast must be sustained partly by maternal blood that enters the lacunae and also by endometrial fluid and cells. On the seventh day the conceptus is barely embedded. Villi are not recognizably started until it is about fourteen days old. During the week intervening, and indeed for several weeks later, while the fetal portion of the placenta is establishing itself, the corpus luteum is maintained, providing increasing amounts of progesterone and estrogen. This perpetuation of the corpus luteum is brought about by a gonadotropin secreted by the trophoblast, the so-called chorionic hormone. The continuance of luteal activity by this fetal hormone substantiates the decidua, which would break down in menstrual disintegration were its supporting hormones, progesterone and estrogen, withdrawn. This must be prevented not only because this tissue with its juices sustains the growing trophoblast but also, perhaps primarily, because it serves as the protecting matrix within which the ever-increasing vascular bed of the maternal part of the placenta is forming.

The versatile trophoblast eventually assumes an added function. At some time between the first and the eighth week of gestation (the twenty-fifth day in monkeys)[33] it takes over the work of the corpus luteum and secretes its own large amounts of progesterone and estrogen throughout the allotted remainder of pregnancy, thus continuing the support of the decidua and the maternal placenta.

Aside from the fact that spermatozoa utilize carbohydrates and produce carbon dioxide, their metabolic processes are almost unknown. Compared to their size they must use a great deal of energy. Do they get their source material from the uterine and tubal fluids? After ovulation the endometrial glands secrete a glycogen-bearing mucus. This comes too late for the fertilizing agents. The food stuffs that are mobilized into and out of the endometrium and the various enzymes and their adjuncts that accomplish this are being studied in several research centers. It will be known in time what are the requirements in their medium for the spermatozoa, and then, doubtless, methods of detecting whether or not essentials are present. In the meantime one can only postulate the necessary presence there of some easily utilizable glucoside, and, in the spermatozoa, the enzymes, adapted for its use.

Cervical Function

The cervix, which constitutes the portio or passage way to the uterus from the vagina, ideally enters this musculated sheath for the functioning penis in the rear of its superior wall, about 8 cm. from the posterior border of the symphysis. So variable are the length of the vagina and the position of the uterus in the pelvis that the portio may lie anywhere in the superior or posterior wall. It never enters from below. Furthermore it may point forward or downward instead of in its normal direction, backward. As can be observed through a glass obturator of a caliber similar to that of the phallus, about 4.5 cm., stretching of the vaginal walls as occurs during coitus brings the attached cervix into the axis of the vagina, except when the portio lies within about 5 cm. of the symphysis. In such cases the penis by-passes it, and ejaculation doubtless hits the posterior wall. Consideration of the following remarks about insemination will suggest that, except when maladaptation is extreme, the position of the cervix is probably of but slight significance. In about any position it can serve its only apparent function, which is to produce a quantity of favorable fluid that, mixing with the ejaculate, still maintains continuity through the canal with the fluid of the fundus.

While estrogen from the growing follicle is causing proliferation of the endometrium, it is also cultivating the endocervical mucosa. Just after

menstruation the mucous excretion from the cervix is scant, very viscous, sometimes even gelatinous and replete with epithelial cells and granular debris. At some time during the week preceding ovulation, when estrogen secretion is mounting, the cervical product increases in amount and decreases in viscosity and cell content. Throughout the phase of ovulation it is normally plentiful, grossly clear as water and of comparatively low viscosity. Careful exposure of the cervix at this time reveals it bathed in this alkaline polysaccharide that before degeneration is easily penetrable to spermatozoa. So copious is the normal production of this fluid that it spreads outward through the vagina and sometimes even rises over the perineal body to bathe the introitus.

Semen

Now, what of the man? Spermatozoa are produced continuously through adult life by the germinal epithelium lining the seminiferous tubules. Fully grown, but immature in some one or several metabolic capabilities required for fertilization, they congregate in the tubules until, with their successors, they are moved out into the epididymis. In the almost interminable coils of this organ the fairly solid mass of closely approximated inactive germ cells is propelled onward, again possibly by the pressure behind of newer organisms, and possibly also by peristalsis of the tubular walls. Here in the epididymis some obscure maturating or complementing process takes place. In the vas the column moves still onward; the cells here also improving, but still more or less inactive, until either those in the van gradually spill over into the posterior urethra to be washed out in the urine or a large part of the whole column is ejected through the ejaculatory duct in the first phase of ejaculation.

As Hotchkiss[34] properly complains, "the exact physiology of the mechanism of ejaculation has not been ascertained." Apparently, within a split second of their arrival, thus, in the posterior urethra, they are joined by a little secretion from the promptly contracting prostate and perhaps vesicles and almost immediately this mixture, made up largely of spermatozoa, is vigorously propelled, ideally, to the cervical os. The total ejaculate varies in amount from about 3 to about 9 cc. and normally contains about 500,000,000 spermatozoa. Recurrently, contractions of the penile muscle discharge the mixed portions, but with each successive ejaculation the concentration of spermatozoa diminishes while the proportion, not the amount, of prostatic and vesicular increment increases.

Thereafter the prostate and vesicles together with the vasa start to replenish their secretions, and the vasa their supply of sperm. The respective characteristic contents of these accessory organs, both in volume and constituents, however, are not reestablished usually within two days, and, in some men past the primal late teens and twenties, possibly not within four days. A second total ejaculation within hours of the first contains comparatively few spermatozoa and a diminished amount of fluid.

Physiology of the male generative tract is still lamentably obscure. (Every gynecologist dealing with infertility should read carefully Hotchkiss's[34] chapters on this subject, for then he can keep both himself and his ethical and conscientious urologic consultant from subjecting distraught and hence credulous couples to plausible but futile, troublesome and expensive procedures and medication.)

The seminal vesicles and prostate function under the influence of the male sex hormone. The former produce a mucoid substance rich in sugars among other chemicals, and sperm have been shown by MacCleod[35] to acquire their energy by utilization of the sugar thus provided. Mention must be made of the enzyme, hyaluronidase, that may be a factor in denudation of the granulosal vestment of the ovum. It is possible that this, or a precursor of it, comes from the secretions of either prostate or vesicles, for it is somehow acquired by the spermatozoa. This subject is further discussed below under "Fertilization."

Furthermore, Chang[36] has recently noted that the ability of rabbit sperm to activate ova may be dependent on some substance contained in the seminal substrate. Perhaps this also comes from some one or other of the accessory male organs. Munro[37] showed that in fowl less than 1 per cent of ova were fertilized by sperm from the testicle, whereas 63 per cent were fertilized by sperm from the efferent ducts. Does the substance postulated by Chang come from the vasa? (As stated above, Finkle[28] proposes that tubal fluid may also improve the effectiveness of rabbit sperm.)

Coitus

Human copulation does not lend itself easily to scientific investigation, and what is known of the process in other mammals is not very helpful. The genital anatomy of human beings is quite different in important details from that of even the other primates. I know of no authoritative description of what actually happens in the human vagina during coitus and at ejaculation nor of the behavior and progress of spermatozoa from the time they leave the penis until one penetrates the ovum. I may therefore be permitted to surmise, trying always to restrain my imagination by a few actual observations.

It may be conjectured that during coitus the recurring thrusts and retractions of the penis cause the vaginal walls alternately to approximate and separate from the portio, thus serving, with the intermittent contact of the glans to cervix, to spread much of the cervical mucus on to the vaginal wall. If this is so, the external os is thus partially cleared of

excess and sometimes opaque degraded secretion such as is commonly seen about the portio. The forceful impact of the first ejaculated mass of spermatozoa and a little seminal fluid against the layer of mucus that covers the deeper vagina and the portio joins these two viscous liquids. Movements of the penis mix them, as continued discharge of alkaline semen containing a few more spermatozoa places such a quantity of material in the vagina as will spread over its walls, when these again become contiguous on withdrawal of the penis. Spermatozoa are thus protected from the usual acidity of the vaginal desquamate.

I do not know what constitutes female orgasm. Perhaps contractions of the myometrium are a component, and perhaps subsequent relaxation contributes a pull on material in the cervix and at the external os. Whether or not this is so is not clearly significant, for there is no doubt that, other factors being adequate, conception is easy without female orgasm.

The stratified epithelium of the vagina is highly absorbent. After coitus some of the ejaculate may be taken up; some is slowly extruded through the introitus as the vaginal walls contract. Active spermatozoa produce carbon dioxide. Gradually, the acidity of the vaginal content is re-established, and after four hours all spermatozoa therein cease motility and probably die.

Insemination

When, as is normally the case, some 500,000,000 spermatozoa are originally present in the fluid that, on withdrawal of the penis, is spread over the vaginal walls, several hundred thousand will by chance find their way into the cervical canal before they succumb.

The mixture of semen with mucus from the cervix is continuous with the column of clear secretion in the cervical canal, as this in turn connects with the thin layer of mucoprotein from the endometrium. Until there is evidence, now completely lacking, that some chemotropic, rheotropic or electrotropic force directs their movements, it must be supposed that spermatozoa swim aimlessly in the widespread vaginal pool, the deepest part of which, containing most of the spermatozoa, is that into which the portio projects when this is normally placed at the end of the vagina.

Observation of the post-coital content of the cervix shows clearly that its secretion at ovulation time offers a very favorable substrate for spermatozoa. In the ovulatory phase, even forty-eight hours after ejaculation, normally progressive organisms are not infrequently seen in great profusion in cervical mucus. About sixteen hours after coitus each high-power field of fluid from within the cervical canal may contain from 10 to several hundred organisms.

At other times in the menstrual cycle sperm from a normal ejaculate may or may not penetrate the cervical product. Occasionally one sees a woman in whom the endocervical mucus almost throughout the cycle secretes a fluid low in viscosity and cellular debris. Penetration by sperm is not as uniform or as extensive as it is normally at ovulation time, nor do those organisms that do enter the cervix apparently find therein a medium that satisfies their needs. They may remain active for twelve or more hours, but usually few are progressively migratory even six hours after coitus.

We may assume that some spermatozoa, highly activated by what they utilize from their ejaculated substrate, still as if aimlessly, find their way from the cervical mucus into the fundus and there deploy. Here is a broad, thin layer of fluid lying between anterior and posterior walls, which connect along the edges in an arc so acute that they would touch one another were it not for the shallow lake of secretion interposed between them. Where the lateral shores of this triangular lake meet the basal fundal border are the two tiny inlets of the tubes. As one watches active spermatozoa in a hanging drop one sees large numbers of the more normal ones gather along the edges, heads out and thrashing tails inward. In this so-called phalanx formation, individual sperm move sideways along the border, sometimes in one direction, sometimes in the other, but in general maintaining their outward orientation. Perhaps by a similar tendency in the uterus sperm may gather along the shore and some of these, perchance, come across the tubal ostia and swim into them.

Progress of sperm in a straight line in cervical mucus has been measured as about 1 mm. per minute. A direct line from the external os to the opening of the tube is perhaps about 120 mm. — a two-hour trip. Spermatozoa were found in the tube by M. Edward Davis[38] about three hours after coitus. If movement is truly random perhaps they move faster in the uterine medium.

In comparison to the size of the spermatozoon, the mass of the cervical and fundal body of fluid together with that in the vagina is so vast as to make it unlikely that a very high proportion of spermatozoa in any single ejaculate ever reaches the tubes. One might guess from the numbers seen in the cervical mucus after coitus that of the several hundred million placed in the vagina, only several hundred thousand reach the cervix. Of these probably some tens of thousands migrate into the fundus, and only a few thousand, at most, eventually enter the tubes.

Here they move upward by swimming against what to their vigor must be a very weak current if it is established only by the cilia of the endosalpinx. The generally downward progress of the tubal fluid — after ovulation, at least — is doubtless accomplished by peristalsis. The waves of this increase in magnitude during the ovulation phase. Just before and perhaps immediately after ovulation, when the necessary spermatozoon, along with

those that accompany it, must find its way to the outer ends of the tube, weaker and more frequent contractions of the myosalpinx might easily form eddies among the irregular rugae of the endosalpinx. In these inconstant but connecting pools the vigorously swimming spermatozoa might, with many slips backward, conceivably be helped onward. Parker[39] has studied the migration of sperm in several species of terrestrial vertebrates (turtle, pigeon and rabbit); in the rabbit, he attributes to the downward ciliary current along the edges of the endosalpinx a reverse central flow that facilitates upward progress. This may be the case in human beings, but, as demonstrated in the film of Somers Sturgis entitled "Observations on Some Factors Which Influence the Direction of Sperm Motility" (1946), the spermatozoa are so enormous and so strong in comparison to the force of the ciliary current, as, apparently, to disregard it. I should think that, if there is any tropism in action, peristalsis is the effective factor.

Of the few thousand spermatozoa from a single ejaculate that might enter the tubes, how many by these theoretical mechanisms reach the ampulla wherein to meet the ovum? Probably not more than a few hundred, or approximately one-hundredth of 1 per cent of the number in the ejaculate. Hence the handicap of oligospermia.

Fertilization

As the inert ovum, still in its ragged zona radiata of granulosa cells, is gently rolled and pushed here and there along the opposing walls of the somewhat dilated outer end of the tube, more than likely, but not inevitably, it encounters a few of the few hundred spermatozoa thrashing about in the ciliary current.

While the second miotic division is taking place — that is, while the second polar body is being extruded from the vitellus, after halving of the number of chromosomes — the zona radiata of granulosa cells is dispersed: denudation of the zona pellucida is accomplished. This may be an important process for fertilization. The multicellular coating of the ovum is desirably removed or else the sperm must have great difficulty reaching the zona pellucida through which one enters the vitellus. The granulosa cells of the zona radiata are held together by a glucoside common to many other cell aggregates or tissues of the body, called hyaluronic acid. This adhesive substance is broken down by the enzyme, hyaluronidase, alluringly found in semen. This very useful agent, possibly also produced by the germinal epithelium,[44, 45] is taken by spermatozoa and freely relinquished whether or not they manifest life.[40] I have watched many human ovarian ova become denuded during culture in human blood serum, in which hyaluronidase is doubtless inactivated. But, like several others, I have also seen granulosa cells of ova in Ringer–Locke's solution leave their fellows while vigorous spermatozoa thrash among them. I had thought that while in culture in vitro, and so possibly in vivo in the tube, granulosa cells died because of separation from the follicular lining and, by resultant proteolysis, lost their cytoplasmic connections, thus dissolving the intercellular matrix by their own degradation products, and so easing their removal by motile sperm. And indeed this may be at least one of the means by which the ovum is stripped. But there is hyaluronidase in or on human sperm,[41] and only a little is needed to dismember hyaluronic acid. This method, then, may be either an essential or merely an adjunctive one. The question is important, for on the answer, as determined by more extensive, controlled experimentation, depends the significance in human fertilization of the presence or of the amount of hyaluronidase in or on the spermatozoa.

Attempts to fertilize mammalian eggs in vitro have been numerous, and successes exceedingly few, and in only two species, the rabbit[42] and the human being,[43] and in only one medium, Ringer–Locke's solution. Is there a substance present in tubal fluid and absent in culture mediums that facilitates fertilization? In some of the invertebrates whose eggs form a fertilization membrane after the entrance of one sperm, the enzyme "fertilizin" is postulated as on, and perhaps in, the egg.[30] This reacts as an antigen to the first sperm that makes contact so as to form a substance that makes impossible the entrance of other sperm heads. Is there present in blood serum and some other body fluids, including semen, an antisubstance that makes penetration of the vitelline membrane by even one sperm, or engrossment of the sperm by the vitellus, impossible? Pincus,[42] working with rabbit ova, and Menkin and Rock,[43] working with human ova, were unable to cause recognizable fertilization of even denuded eggs in blood serum.

* * *

It must be concluded from the foregoing discussion that much remains to be learned about how human beings reproduce. This ignorance is not fatal, for fortunately the intricate process does not require carefully executed managerial control — that is, when the delicately adjusted and integrated mechanism functions normally. Furthermore, perfection in each unit is not always required for in many details there is a fortunate leeway of error. On the other hand, when an apparently healthy copulating couple fail to reproduce, knowledge of required physiology is necessary for success. Knowledge is also requisite for faultless and harmless prevention of conception, which human reason clearly manifests is an indispensable factor for the health, wholesomeness and progress of human society. Intensive research will bring rich rewards that will greatly facilitate the elevation of fallen man.

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CASE RECORDS OF THE MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

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CASE 35201

PRESENTATION OF CASE

First admission. A twenty-one-year-old barber was admitted to the hospital complaining of crampy abdominal pain.

Three years before admission the first episode of low abdominal cramps appeared. There was no obstipation or vomiting. He was hospitalized for two days. The second attack occurred twenty-seven months before entry. He was hospitalized; an appendectomy was performed. He was well until four months later, when nausea, vomiting and jaundice appeared without any severe abdominal pain. He was hospitalized for three weeks, at the end of which the jaundice had disappeared. Following discharge he began having episodes of crampy lower abdominal pain, with constipation for two or three days, which then subsided for symptom-free intervals of about a month, to be followed by similar episodes. There was no nausea or vomiting with these attacks. The attacks over the three-year interval had a persistent pattern. The cramps, definitely lower abdominal, were increased by ingestion of food. The symptoms were accentuated as the day progressed. A prodrome of "tightening up" in the lower abdomen preceded cramps. Constipation with the cramps was usually relieved by enemas. Between attacks the appetite was fair, there was no indigestion, the bowels moved daily, and there was no melena or hematemesis. One week before admission an attack recurred with the usual lower abdominal cramps, constipation and the inability to pass flatus. Several enemas helped a little, and mineral oil three days before entry gave him some loose movements. In the two days before admission there were no further bowel movements; nausea and vomiting appeared for the first time and persisted. He vomited solid foods but was able to retain liquids. The abdomen did not become distended.

Physical examination showed a thin, slightly dehydrated man in no distress. The chest was normal. Spasm of both rectus abdominal muscles was present. There was no tenderness or masses and no distention. Occasional high-pitched peristaltic tinkles were heard. A well healed appendectomy scar was seen. Rectal examination was negative.

The blood pressure was 130 systolic, 70 diastolic.

The white-cell count was 16,000. The hemoglobin was 14.8 gm. The urine was normal. The stools were repeatedly guaiac negative. The serum total protein was 7 gm. per 100 cc. The cephalin-flocculation test was ++ in twenty-four and forty-eight hours. The gastric contents were guaiac negative, and free acid was present. The sedimentation rate was 5 mm. in one hour. The blood Hinton test was negative.

A plain film of the abdomen and barium enemas demonstrated no abnormality. A gastrointestinal series, including small-bowel examination, was negative. The Graham test showed good concentration, and contraction after a fatty meal. No stones were seen. Proctoscopy and sigmoidoscopy showed no abnormality.

While in the hospital the patient was afebrile. On a soft diet and cathartics the symptoms decreased in severity. The white-cell count returned to normal. He was discharged on the tenth hospital day. A full diet supplemented by mineral oil and metamucil was prescribed.

Second admission (one week later). He re-entered the hospital with a recurrence of severe lower abdominal cramps and constipation of three days' duration. There was no change in the objective findings since discharge.

An operation was performed.

DIFFERENTIAL DIAGNOSIS

DR. EDWARD HAMLIN, JR.: This case seems unusual for one of these exercises in that there is a complete lack of red herrings or any positive information. I think it would be helpful to see the films.

DR. STANLEY M. WYMAN: There is very little to add to the written description. The plain film of the abdomen reveals no unusual soft-tissue shadows and no evidence of intestinal obstruction. I can see no definite stones. Films after the Graham test show no organic abnormality. The barium enema and the gastrointestinal series show, as far as I can see, a normal large bowel, stomach and duodenum, and on these two films taken at one and two hours, respectively, a normal-appearing jejunum and ileum.

DR. HAMLIN: That is no help either.

We have, then, to explain the cause of lower abdominal cramps that eventually required an operation and, in a young, apparently otherwise healthy person, had occurred intermittently and perhaps increasingly over a period of three years. One examiner, at least, had the opportunity of exploring the abdomen and removing the appendix, but apparently the cause of the present difficulty was not noted even though presumably the difficulty

had been present before. The episode of jaundice, we will do well to discard and call some form of infectious hepatitis because, at that time at least, the symptoms of which he had previously complained and of which he later complained apparently were in abeyance.

Lower abdominal, crampy pain usually means large-bowel involvement, and the causes of lower abdominal crampy pain as applied to large bowel would mean some degree of subacute intestinal obstruction. Volvulus is something that one should think of, but I certainly see nothing in the films that looks like volvulus, nor do I see anything that looks like subacute intestinal obstruction. There are many other possibilities in the large bowel. One can run through a list of them, only to say that the normal barium enema, negative proctoscopy and sigmoidoscopy should effectively rule them out. They are not necessarily ruled out by such procedures, but for our purposes we must assume that they were. Small-bowel difficulties can also cause crampy low abdominal pain. Usually, pain in the small bowel is referred to the region of the umbilicus; disease of the lower end of the ileum, however, may cause, as most of us have seen, pain referred to the lower abdomen. Since the roentgenologist has a far more difficult job to rule out disease in the small bowel than in the large bowel, and since proctoscopy and sigmoidoscopy do not reach that far, it would perhaps be politic to confine our attention to the lower small bowel. It would seem at least unusual to have to examine the intestinal tract any higher than that.

What other possibilities of subacute intestinal obstruction have we to consider? The description is certainly that of a low order of intestinal obstruction. What are the possibilities of such an obstruction existing in the face of no increase in distention noted on several occasions, and no increase of air in the small bowel as seen on x-ray study? The only evidence is the subjective impressions of the patients, and it was mentioned that occasional high-pitched peristaltic sounds were heard. Again, one can run through a long list of possible lesions. We can, however, restrict ourselves to a lesion that had existed for at least three years, which will rule out a good many conditions or make them at least much less likely. For my own sake, I cannot see the point of running through a long list except from a statistical point of view. Certain things can be ruled out or partially ruled out, such as lymphoma, which should have produced blood in the stools on some occasion, although it might have existed for three years. A lipoma or large polyp of the small bowel could produce such symptoms. I expect, however, over this period of time that some bleeding would have been noted at least microscopically. The one best entity that I can think of that would be chronic and that would produce very slowly increasing symptoms would be a constricting lesion of the small bowel, which produced symptoms only when some intercurrent irritation of the bowel was present, and, of these, the best example that occurs to me is carcinoid.

DR. JACOB LERMAN: The results of the barium enema need not rule out volvulus. The bowel could unwind in a few hours.

DR. HAMLIN: Yes, but a redundancy of the sigmoidal loop is usually seen. Certainly I do not think one can rule out anything with the data as presented, but I think volvulus is unlikely.

DR. ALFRED KRANES: Was the original appendectomy done here?

DR. TRACY B. MALLORY: I think not.

DR. HAMLIN: I should also mention Meckel's diverticulum as a possibility.

DR. MALLORY: Dr. Ellis, you saw this man.

DR. DANIEL S. ELLIS: Yes, but as Dr. Donaldson's patient. I saw him in consultation. He had been followed outside by one or two doctors, who had become desperate because of the recurrent attacks, and they sent him down here for surgery. I saw him and decided that the history was not very definite. I did not see him in an acute attack in the first hospital admission, and I was of the opinion that he probably did not have anything but "gas pains," but that if he did have something, Meckel's diverticulum was the most likely possibility. I was largely responsible for saying that he should not be operated on at the time of the first admission but that he should be sent home with definite rules to follow and that, if he continued to have pain, he should be explored even though we might not know at that time what he had. I thought it important to be absolutely sure in view of recurrent attacks that there was not something that might be cured by surgery if attacks continued. They did, and he was explored.

DR. GORDON A. DONALDSON: The family physician was the only one who really knew what should next be done for this patient – and that was to be a diagnostic exploratory laparotomy. However, he had had the chance, as Dr. Ellis pointed out, to see him in an acute attack. During the first admission the patient had had no acute pain, so we did a proctoscopy and a sigmoidoscopy because the pattern of his pain pointed to the large bowel, as Dr. Hamlin has said, and we had a very good view of the large bowel both from proctoscopy and barium enema. It was low abdominal crampy pain, which we associate only with large-bowel lesions. The other point was that the patient was constipated and had been constipated for some time and had taken a high-carbohydrate diet; it was believed that he might have nothing other than constipation. Sure enough, he was home for only three days, long enough to become constipated again, when he appeared for the second admission. On two consecutive days he again had pain after eating. We

finally did an exploratory laparotomy as a diagnostic procedure.

DR. HAMLIN: The implication is that we are descending the bowel. I cannot descend it with you though.

CLINICAL DIAGNOSIS

Meckel's diverticulum?

DR. HAMLIN'S DIAGNOSIS

Carcinoid of small bowel.
Meckel's diverticulum?

ANATOMICAL DIAGNOSIS

Persistent omphalomesenteric duct, with focal ulceration, probably peptic.

PATHOLOGICAL DISCUSSION

DR. DONALDSON: I would like to draw a diagram of the lesion. It was something I had not seen in an adult, although at the Children's Hospital it is seen occasionally. This is a lateral view of the abdomen, with the navel in the center, and this is a loop of small bowel. About 60 cm. from the ileocecal valve (where it should be), there was a patent tube-like structure measuring 25 cm. in length and 1 cm. in diameter, running from the ileum to the umbilicus. There was a good deal of thickening near the umbilical end, and this was important in view of the symptoms.

DR. MALLORY: This tube, which was resected, was lined with intestinal mucosa of the small-bowel type. At one spot was an area of ulceration, which looked very characteristic of peptic ulcer, although in several sections we were not able to identify any gastric endothelium. I think probably it was present, and we missed it in picking out blocks for sectioning. The diagnosis, of course, is obvious – a persistent omphalomesenteric duct, which is much less common than the usual Meckel diverticulum projecting a short distance from the intestine. The origin of both is similar, of course.

CASE 35202

PRESENTATION OF CASE

A seventy-four-year-old man was admitted to the hospital because of abdominal pain of three days' duration.

The pain began suddenly following the ingestion of a small amount of food. It was severe, was localized to the right lower quadrant and came in waves. There was associated nausea, and dark-green material was vomited. The pain persisted with slight diminution in severity. He had one stool and passed gas by rectum. The patient had always been constipated and took laxatives frequently. Several times recently he had noted tarry stools. Seven years before entry an acutely inflamed appendix had been removed, and a wound abscess had complicated recovery. Three years later a defect in the appendectomy scar and a right inguinal hernia were repaired. A year and a half before admission the patient had five or six episodes of severe epigastric pain. Following one of these episodes he was admitted to another hospital with vomiting and abdominal distention. A serum amylase of 500 units per 100 cc. was found. A cholecystectomy was performed. The gall bladder contained many small stones, and the common duct was large and much thickened but contained no stones. The pancreas appeared to be thickened, but no areas of fat were visible. He recovered uneventfully and was well until four months before entry, when he was again hospitalized with a picture of intestinal obstruction. The serum amylase again was elevated. There was prompt recovery on conservative therapy. Guaiac tests on the stools were 0 to ++++ on several occasions. A barium enema showed no abnormality of the colon. He was readmitted to the hospital two weeks later when he had a sudden onset of pain radiating across the abdomen. There were fever, leukocytosis and an elevated serum amylase. On the sixth hospital day he felt something "give away" in his abdomen, and he was immediately relieved. A gastrointestinal series showed a small hiatus hernia. The stomach and esophagus were normal. The duodenal cap was intrinsically normal, but the bulb, although normal in size, showed an abnormally smooth contour to the inner loop, questionably encircling a mass. Also, a questionable filling defect of the mid-transverse colon, not previously seen, was noted on barium enema.

Four weeks before entry "operation for strangulated umbilical hernia" was performed at another hospital. He remained well until the present episode.

On physical examination the chest was emphysematous. There was a Grade II, precordial systolic blow. The abdomen was distended, more so on the right, and was moderately tympanitic.

Tenderness and spasm were present over the entire abdomen, most marked in the right upper quadrant, where a large, smooth, tender mass, 15 to 18 cm. in diameter, was felt. The mass seemed to be continuous with the liver. Peristalsis was diminished. Rectal examination was negative except for an enlarged prostate.

The temperature was normal.

The urine specific gravity was 1.017, a trace of sugar was present, and the test for albumin was ++. Many granular casts and 5 pus cells per high-power field were found in the sediment, which gave a ++ test for bacteria. Examination of the blood showed a hemoglobin of 13.8 gm. The white-cell count was 12,000, with 82 per cent neutrophils. The nonprotein nitrogen was 66 mg. per 100 cc. The van den Bergh reaction was 0.8 mg. per 100 cc. direct and 1.4 mg. indirect. The stools were guaiac negative. A plain film of the abdomen showed no obstruction.

Auricular fibrillation was noted a few hours after admission. The pain, vomiting and distention persisted. On the second hospital day one observer felt a mass in the right upper quadrant, which was believed to be attached to the liver. On the third hospital day the patient suddenly cried out with pain and vomited, and the abdomen became rigid and silent. Preparations for operation were made. As anesthesia was given, the patient suddenly became pulseless, and respirations soon ceased.

Differential Diagnosis

Dr. Richard Warren: It is significant that the pain was in the right lower quadrant. It is important to note that the sequence of events began a year and a half before entry. I believe that the seven-year and three-year episodes can be put down as separate diseases or separate episodes in this man's history.

May we see the x-ray films?

Dr. Stanley M. Wyman: This is the only film available. It is a plain film of the abdomen taken after admission and shows the gas-filled cecum, the transverse colon and the splenic flexure. I cannot see the descending colon or rectum. There are no dilated loops of small bowel and no unusual areas of calcification.

Dr. Warren: Is there any evidence of fluid or gas?

Dr. Wyman: I cannot be sure that there is free fluid or gas in the abdominal cavity. The film was taken with the patient in an upright position. I am not much help.

Dr. Warren: In discussion of this case I would first like to take up the point of whether or not the patient had something new on this admission or whether what he had was a direct extension of the previous symptomatology. When he entered this hospital the trouble was in the right lower quadrant for the first time. A serum amylase was not done so it raises a little doubt whether the patient had something new or whether it was a continuation of the old symptoms. However, the discussion of the case can best be centered around the question of whether or not he had pancreatitis. I would like to point out the things in favor of pancreatitis and those against it. The pain came on after the ingestion of food. Pancreatitis is supposed to come on after dietary indiscretion, such as overeating of food. This one came on with the eating of food in small quantities. Pain in the epigastrium on the previous admission is in favor of it also. Above all we have the operative findings. The gall bladder was removed; the pancreas was found to be thick, and there was disease of the common duct. They are the most cogent features in the past history. The x-ray films showing extrinsic pressure on the duodenum and transverse colon are in favor of pancreatitis, as is the presence of a tender inflammatory mass in the upper abdomen. The patient did not have much infection and the low white-cell count and normal temperature could be perfectly consistent with pancreatitis. The polymorphonuclear ratio is not recorded, nor is the pulse.

Dr. Benjamin Castleman: The patient was in for only three days on the last admission. The pulse was 80 on admission, but went up later to 100.

Dr. Warren: That does not mean a great deal except that he did not have an overwhelming infection. Finally, the elevated serum amylase, which was determined at the other hospital and repeated here, is overwhelming evidence in favor of pancreatic necrosis.

What do we have against pancreatitis or pancreatic disease? We have a history of tarry stools. We have a ++++ guaiac test on the stool on the previous admission. This might be thought to be some evidence against pancreatitis. However, I believe that it is consistent with it, particularly an inflammatory lesion with presumably enough congestion of the gastrointestinal region to cause bleeding. I have recently seen a patient who had

pancreatitis who was a problem in differential diagnosis because of the fact that he had tarry stools. Because of the blood in the stools many people thought that it was not consistent with pancreatitis. I am sure that it is. I cannot explain right-lower-quadrant pain in pancreatitis. The absence of back pain in pancreatitis of this degree is very unusual. The abstract does not say that it was absent; it merely does not mention it. The mass on the right side of the abdomen is unusual for pancreatitis. An inflammatory mass in pancreatic necrosis is most often in the midline or on the left in my experience. The absence of fat necrosis at the preceding operation throws a little doubt on the diagnosis. How far fat necrosis was looked for, I do not know. Fat necrosis in pancreatitis is classically behind the pancreas in the retroperitoneal area below the transverse colon. We are not told whether or not that area was inspected.

What else do we consider in differential diagnosis besides pancreatitis? The question of intestinal obstruction is brought up often in the history. The patient had previously been operated on for inguinal hernia, which makes me think of intestinal obstruction. I believe the x-ray examination rules out any significant degree of small-bowel obstruction. The fact that he passed gas and had a bowel movement during the three days of his illness is also against it. Peritonitis from perforation of a gastroduodenal lesion cannot be ruled out. He had a gastrointestinal series three months previously. Could some other viscus have perforated? The colon, possibly. In view of the history I do not believe that is likely.

How about the possibility of a vascular accident? Auricular fibrillation was noted. If we are going to assume a vascular accident, we must assume that he had something within the abdomen. He could not possibly have had repeated emboli to this region for a year and a half. Could he have had thrombosis of the celiac axis or the splenic artery? That might explain the final episode, but certainly it could not explain the long-standing history. The mass was always recorded as being contiguous with the liver. What condition in the liver could cause a mass of this nature? Could the patient have had a pylephlebitis coming from pancreatitis and a large abscess perforating from the liver into the right gutter? That is unlikely, I think. Cancer of the pancreas or of the bile duct in the absence of jaundice is unlikely. As far as I am concerned I can make no other diagnosis than that of acute pancreatitis with abscess. I believe that death was due to rupture of this abscess into the peritoneal cavity. Presumably, the marked degree of collapse was due to the liberation of tryptic ferments from the abscess into the peritoneal cavity.

DR. SEDGWICK MEAD: Dr. Warren, do you have any explanation for the episode when the patient felt "something give way" and then felt better?

DR. WARREN: I purposely skipped over that because I could not explain it. That is in favor of intestinal obstruction, but there are so many other things in favor of pancreatitis here that I really must make that diagnosis.

CLINICAL DIAGNOSES

Metastatic carcinoma.
Perforated viscus.

DR. WARREN'S DIAGNOSIS

Acute pancreatitis, with abscess formation and rupture into peritoneal cavity.

ANATOMICAL DIAGNOSES

Pancreatitis, acute and chronic, with pseudocyst formation.
Erosion of superior pancreaticoduodenal artery.
Hematoperitoneum, severe.
Squamous-cell metaplasia of pancreatic ducts.
Adenomatous polyp of colon.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: When the abdominal cavity was opened the first thing that the prosector found was a large mass of blood clot in the right upper quadrant, going under the liver as well as over it. Most of this blood was old, but there was also a great deal of fresh blood, some of which was not clotted. It was estimated as being over a liter. I think we can assume that that was the immediate cause of death — that is, exsanguination into the abdominal cavity.

Further exploration revealed blood in other parts of the abdominal cavity, fresh rather than old. This blood was coming from a large cyst, which involved the entire head of the pancreas, or at least

involved the region where the head of the pancreas should be. This cyst was about 12 cm. in diameter, and on its superior aspect was a hole from which blood apparently had escaped into the abdominal cavity. When this cyst was opened the lining was found to be shaggy and covered with fibrin and old blood. On the posterior aspect of this cyst there was a small blood clot that blocked the opening of a large artery, which was found to be the main superior pancreaticoduodenal artery. We have, then, erosion of an artery into this cyst and rupture of the cyst superiorly into the right-upper-quadrant region and the abdominal cavity. There was also another smaller cyst just to the left, which involved part of the body of the pancreas. The tail and rest of the body of the pancreas were firm and on sectioning showed the normal lobular architecture. The pancreatic duct was dissected beginning at the tail and found to end abruptly in scar tissue just about where the cyst began; when dissected from the ampulla, it was patent down to the same spot behind the cyst. So there was obliteration of the pancreatic duct in its mid-portion for a distance of 12 cm. Sections of the cyst showed just fibrous tissue without any epithelium. Sections of the body and tail of the pancreas showed a mild inflammatory reaction, mostly monocytes and lymphocytes and a few polymorphonuclears. Most of the pancreas was fairly intact. The ducts, however, showed a very severe degree of squamous-cell metaplasia, which according to Rich* may be a factor in the cause of pancreatitis — that is, the heaped-up squamous cells blocked the smaller ducts allowing for seepage of the ferments into the parenchyma to produce pancreatitis. Whether that was the primary disease here or a secondary change due to the block caused by the cyst, I do not know. With long-standing obstruction in any duct, squamous-cell metaplasia may develop. I believe these cysts originated from previous necrosis of the pancreas and were "so-called" pseudocysts of the pancreas rather than true neoplasm. When the pseudocysts appeared, I do not know. Certainly they were not present a year and a half previously, when the patient was operated on by Dr. McKittrick, who examined the pancreas very carefully and found nothing but a thickened pancreas and no fat necrosis. We found fat necrosis all over the abdomen. It is possible that what "gave way" was one of the pseudocysts, which relieved the tension in the pancreas.

DR. WARREN: There was no suppuration in the pancreas itself, just two hemorrhagic pseudocysts?

DR. CASTLEMAN: That is right.

DR. WARREN: Did the pancreatic duct communicate with the cyst?

DR. CASTLEMAN: No. The patient also had an adenomatous polyp in the colon which may account for the positive guaiac test in the stools.

*Rich, A. R., and Duff, G. L. Experimental and pathological studies on pathogenesis of acute hemorrhagic pancreatitis. *Bull. Johns Hopkins Hosp.* 58:212-259, 1936.

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A NEW VIRUS DISEASE

DURING the past few years several new nonbacterial infections apparently transmitted from animals have been described in human beings. Notable among respiratory infections have been psittacosis (ornithosis), which is transmitted from birds, and Q fever, apparently acquired from cattle. Evidence that a new virus disease of fowls, which has recently been recognized as highly prevalent in the United States, may be transmitted to human beings and may be spreading in some parts of this country has recently been presented by workers of the United States Public Health Service.*

In 1926, a highly infectious and fatal disease of fowls was recognized in the Dutch East Indies and at about the same time at Newcastle-on-Tyne. In England a filter-passing agent, designated as Newcastle disease virus was isolated from infected birds in the following year. Similar outbreaks were soon described from various parts of the world outside the United States, but it was not until 1941 that a disease of chickens was recognized in California under the name of avian pneumoencephalitis. The disease in fowl is usually characterized by neurologic symptoms in immature birds, whereas respiratory manifestations predominate in the adults. This disease was subsequently shown to be caused by a virus similar to the one that causes Newcastle disease. Systematic surveys subsequently demonstrated the presence of the disease in almost all parts of this country. It has therefore become of major importance to poultry men throughout the world.

Many groups of workers have studied the Newcastle disease virus. It has been found possible to propagate the virus in embryonated hens' eggs, and the infection has been transmitted to some laboratory animals by intracerebral inoculation. It is of interest that this virus has the ability to agglutinate chicken red cells just as the influenza and mumps viruses do. Although many workers have handled both the virus and infected fowl tissues, there have been very few reports of human infections. All the previously recorded human infections with this agent seemed to involve the eyes and had resulted from accidental laboratory infections.

Although the Newcastle disease virus was first recognized in California in 1941, it was not reported in the eastern states until 1944–1945, and it was at about this time that certain atypical cases of human infection began to appear in Tennessee. Furthermore, the disease in fowl was not described in Alabama and Tennessee until 1947, although it may have been present earlier, and apparently some human infections also began to appear in Alabama in 1948 or perhaps late in 1947.

Howitt, Bishop and Kissling, working in the virus laboratory of the Communicable Disease Center that the United States Public Health Service operates in Montgomery, Alabama, studied serums received in 1947–1948 from various groups

*Howitt, B. F., Bishop, L. K., and Kissling, R. E. Presence of neutralizing antibodies of Newcastle disease virus in human sera. *Am. J. Pub. Health* 38:1263-1272, 1948.

of children in Alabama and Tennessee who had suffered from a mild and brief central-nervous-system infection that had left no sequelae. Some of the patients were thought to have some form of encephalitis, and others were considered as having nonparalytic poliomyelitis.

Because of a history of frequent association with chickens and the absence of antibodies for common neurotropic viruses, these workers did neutralization tests with these serums against the virus of pneumoencephalitis or Newcastle disease of fowl. Of 15 serums from children in Tennessee with this new clinical syndrome, 12 showed antibodies for the virus of Newcastle disease. One case of encephalitis and one with a poliomyelitis-like syndrome also had antibodies for this virus. Numerous other serums that had been obtained in previous years from children without this atypical syndrome were negative. Two chickens from the premises of one of the patients showed both the pathological lesions of Newcastle disease and the presence of neutralizing antibodies in the blood. Serums were also obtained from 10 human cases of a mild central-nervous-system syndrome in rural areas of Alabama, and 8 of these showed definite neutralizing antibodies for the virus of Newcastle disease, and chickens with similar antibodies were also found in association with several cases.

After work with the virus was started in the Montgomery laboratory, an acute influenza-like infection developed in 6 of the laboratory personnel. Antibodies in high titers against the virus of Newcastle disease were found in the serums of these 6 persons. In addition, antibodies were found in 4 of 11 serums from laboratory personnel without symptoms. Serums obtained from 19 people before the virus work began showed no such antibodies. However, the blood of 3 persons who had typical symptoms before they came to the laboratory also showed neutralizing antibodies for Newcastle disease, whereas neutralization tests were negative on serums obtained earlier from many children and adults who had not shown these atypical neurologic symptoms.

Although no virus has yet been isolated from any of the human cases in this country, Howitt and her co-workers believe that their evidence indicates that the virus of Newcastle disease of fowls is probably the agent responsible for many of the atypical central-nervous-system infections that have been reported in man during the past few years. They also suggest that, as in fowl, the manifestations are neurologic in young persons and influenza-like in adults. They believe that the virus originating with fowls has probably spread to man, and their evidence suggests that in many cases there is a man-to-man, rather than fowl-to-man, dissemination of the disease.

NO HOLDS BARRED

THE Committee for the Nation's Health, in a characteristic release, continues its compaign of disparagement against the American Medical Association. Since the Association is the accepted agent of a large majority of the practicing physicians of the United States, who are currently expressing their approval of its present policies in a very tangible manner, this campaign has the effect of reflecting on their judgment.

The Committee for the Nation's Health, under the chairmanship of a former president of the Massachusetts Medical Society, scrutinizes in this release the relations between the American Medical Association and the National Physicians Committee, suggesting that the American Medical Association may be blowing both hot and cold. It happens that nothing particularly new has developed in these relations. Since the formation of the National Physicians Committee over ten years ago, it has had the general approval of the American Medical Association, and this general approval has at no time been withheld. Within a matter of months the objectives of the National Physicians Committee have also been approved by the Council of the Massachusetts Medical Society.

The National Physicians Committee, during the course of its activities, has made some palpable mistakes. So have the American Medical Association and the Congress of the United States and so have most, if not all, of the persons comprising our somewhat disturbed society, if given the opportunity. Even the Committee for the Nation's Health, granted a long enough rope and enough time, may some day be in error.

The Committee for the Nation's Health continues its allusions to the "slush fund" of the American Medical Association, employing suggestion as a substitute for evidence; it crows over the news that Whitaker and Baxter, in dutiful compliance with the law of the land, have registered as lobbyists. Congress, it may be hoped, will not be unduly disturbed over the implication that the profession of lobbying, which it has legally recognized, is somehow not respectable.

The physicians, at least, on the Committee for the Nation's Health, are aware that the profession to which they are devoted is under heavy fire. Regardless of whether, in their devotion, they believe that it requires a major operation or can recover through more conservative treatment, they must admit that the argument cannot be fairly settled with six shooters on one side of the table and water pistols on the other.

CORN FOR INSTANCE

NEWSPAPER headlines and magazine digest articles that keep the public informed concerning scientific progress make it hard for the family medical adviser to remain a jump ahead of his patients. For example; what is monosodium gluconate; is a diet of rice and pineapple juice "good for you"; what about salt substitutes; does the television tube emit enough gamma rays to warrant concern over its possible harmful effects on the family; can oranges be bought to better advantage by the pound or the dozen; is painless childbirth possible without anesthesia; and, perennially, should canned foods always be immediately emptied into a dish when the tin is opened?

One might suppose that housewifely concern over the supposed dangers of canned foods had been completely quieted, now that perhaps three fourths of the food comes from tins and the younger generation has almost universally learned to prefer canned peas to the violently green fresh variety that seems to please their elders. But enough vague fear of what may happen to food left in the opened tin persists to impel the manufacturers of tin cans to publish accurately documented scientific information about the healthfulness of the products sold in their containers. These products are sterilized in the tin, which may or may not be lined with a coating of enamel; in any case no harmful interaction occurs between food and container, and the food is more apt to stay sterile and harmless if left in the clean open tin (provided it is kept cool and covered) than if placed in a dish of questionable sterility and left exposed. Eye appeal may be enhanced if the food is placed in an attractive bowl, but hygiene does not require the transfer.

HEALTH ACCESSORIES

BRITAIN'S bald heads of both sexes, according to a recent statement in *Newsweek*, will soon be demanding Government-financed wigs at the rate of 100,000 a year. The estimate has been made by the two dozen busy wigmakers currently engaged in supplying utility wigs, at $40, and non-utility wigs, at $50, for the Ministry of Health.

Two styles of wigs are furnished for men, full wigs or "sculpettes," and five for women. Each applicant is allowed two wigs at $40, creating a possible demand that may cost the Government $8,000,000 annually; in addition, cleaning and dressing the spare wig every two months (another Government obligation) will add $400,000 to the bill.

Under other provisions of the National Health Act false teeth, hearing aids, trusses, electric wheel chairs and spectacles are supplied to a grateful public. November estimate of the Ministry of Health was that 1,700,000 pairs of glasses had already been issued. An applicant was unsuccessful, however, in procuring a free bottle of hair shampoo.

MASSACHUSETTS MEDICAL SOCIETY

DEATHS

HEFFERNAN — David A. Heffernan, M.D., of Brighton, died on April 18. He was in his sixty-ninth year.

Dr. Heffernan received his degree from Harvard Medical School in 1902. He was a member of the New England Otological and Laryngological Society and a fellow of the American Medical Association.

His widow survives.

SMITH — Lillian R. Smith, M.D., of Harwich, died on April 13. She was in her sixty-fourth year.

Dr. Smith received her degree from Tufts College Medical School in 1917. She was formerly director of Maternal Health and Child Hygiene in Michigan and was in charge of the Emergency Maternal and Infant Care Program in that state during World War II. She was a fellow of the American Academy of Pediatrics and the American Medical Association.

A sister survives.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

RHEUMATIC-FEVER FELLOWSHIPS

The United States Children's Bureau has made available through the Massachusetts Department of Public Health and the Harvard Medical School one fellowship in rheumatic fever at the House of the Good Samaritan of the Children's Medical Center, Boston, for the year beginning July 1, 1949.

Applicants should be interested in working eventually in the field of rheumatic fever in public health or in teaching, rather than in private practice.

Work under this fellowship will probably be acceptable for credit by the American Board of Internal Medicine or the American Board of Pediatrics.

Application should be made as soon as possible to Dr. Benedict F. Massell at the House of the Good Samaritan, 25 Binney Street, Boston 15 (telephone, BEacon 2-3002).

REPORTS OF RESEARCH PROJECTS IN PROGRESS

Division of Biologic Laboratories

In this division, field studies in medical students and Army personnel in collaboration with the staffs of various medical schools, hospitals and other groups in Greater Boston regarding diphtheria immunity in adults are continuing with the support of a Government contract; studies of immunity in diphtheria patients in collaboration with the staff of Boston City Hospital are still in progress; in the chemical and immunologic studies on purification of diphtheria toxoid, begun in 1944 and continuing to date, various methods have been employed, and recent results have produced a toxoid almost 100 per cent pure and considerably more potent than the starting material (studies are also under way on methods for more exact measurement of the potency of diphtheria toxoid); for the past five years a long-term study on the stability of biologic products has been in progress, directed toward elimination of unstable lots and discovery of stabilizing substances; studies of newly reported methods of rapid diagnosis of smallpox have been undertaken, for possible use in an emergency; in conjunction with the development of pertussis vaccine, studies have been instituted on the blood-cell clumping factor in pertussis cultures, on the toxic factor in culture supernatants and on other significant properties of pertussis preparations; about 1600 liters of outdated plasma have been fractionated, laboratory and clinical tests on albumin and gamma globulin prepared from this source having shown both fractions to be fully as effective as the products made from fresh plasma (this finding opens the way to a major and hitherto undeveloped field of blood fractions); under grants from Research Corporation totaling $41,940 (July, 1945, to June, 1949, inclusive) a program for testing blood fractions made under license from the Cohn patents has been conducted and has included tests on numerous major and minor products, and assistance to miscellaneous studies.

Division of Cancer and Other Chronic Diseases

In this division, an effort is being made to evaluate detection-center activities, to measure screening by means of the seven danger signals and to ascertain the incidence of cancer among persons with and without any of the seven danger signals; a six-year evaluation of the cytology test for cancer, which is more than half completed, will answer many questions regarding procedures and will determine the value of the test itself; a study is underway showing environmental factors in relation to the length of life of patients after visiting a cancer clinic; in a long-term study on environmental factors in relation to the etiology of cancer one report is in the process of being published, and others are nearly ready (cancer of the breast, cervix and skin are being studied at present; a continuation project on familial aspects of cancer that has been in progress for several years embraces the possible etiologic effects of heredity, conjugal state, number of children and so forth; the accuracy of the death record in respect to certain chronic diseases is constantly under study and will continue until maximum results have been obtained (work has been done on heart disease, cancer, diabetes, nephritis, arteriosclerosis and rheumatism); since at present certain sites of cancer show an upward trend in death rate and others a downward trend, and still others are trendless, twenty sites are being watched, and future changes in their trends will be reported; the best mediums and the various channels for propaganda purposes, for creating awareness and for stimulating patients to action if symptoms of cancer appear are being evaluated.

Division of Communicable Diseases

In this division, a bacteriologist assigned to the Virus Laboratory at Harvard Medical School is working on the laboratory aspects of the diagnosis and epidemiology of poliomyelitis; a study to determine the feasibility of giving booster doses of diphtheria toxoid to high-school students is underway; records of all cases of typhoid fever reported since 1940 are being thoroughly analyzed; the titers of naturally occurring anti-A and anti-B isoimmune bodies in the serum of persons donating blood to the mobile blood bank are being studied; the presence, type and titer of Rh antibodies in the serums of Rh− persons who have received transfusions of blood not typed for the Rh factor are being investigated; studies directed toward improving the mediums and methods of culturing of tubercle and diphtheria bacilli and enteric pathogens are underway; and the laboratory, in co-operation with the Influenza Information Center, National Institute of Health, is performing serologic tests on blood specimens from persons suspected of having infections with either influenza A or B viruses.

Dental Division

Observations on the clinical effect of the use of a fluorinated dentifrice on the incidence of dental caries in 3000 school children are in their second year in two separate locations; fluorination of the water supply of two state schools is now in its third year of operation, and a yearly check on the incidence of dental caries is being kept by investigation of the rates of decayed, missing and filled teeth (nutritional studies are being included).

Food and Drug Division

The effects of the addition of water upon food value and keeping qualities of shucked clams by the various methods of washing, as practiced in clam-shucking plants, are being studied; new, sensitive, qualitative test for the detection of glycogen in horse meat is being investigated; the stearin derived from beef fat, horse fat and pork fat, or mixtures of these fats, is being identified microscopically, and the specific volumes of the hemicellulose content of soy flour in frankfurters is being determined; the analytical constants to determine genuine qualities of cider and other vinegar are being evaluated; the possibilities of a rapid sorting test for the initial separation of samples of enriched flour from those of unenriched flour are under investigation; the methods of identification of the newer synthetic narcotic drugs are being studied; a new, sensitive method for the detection of urea-formaldehyde sizing in garnetted clippings or shredded cloth is being developed, and analytical procedures for differentiation of new and second-hand bedding filling materials are being evaluated.

Division of Maternal and Child Health

The activities of this division include performance of the Massachusetts hearing test (a successful and inexpensive adaptation of pure-tone-testing methods to large groups of children), a study of the relation of stereopsis to muscular co-ordination and educational adjustment of children, the Harvard pediatric study of the incidence of illness and the types and costs of pediatric care and the maternal-mortality study conducted by the Committee on Maternal Welfare of the Massachusetts Medical Society.

Division of Sanitary Engineering

In this division the following matters are being investigated: trickling filters, with emphasis on rates of B. O. D. removal, effects of recirculation, size of filter medium, oxygen requirements and physical design; disposal of trickling-filter effluents on intermittent sand filters; design and operation of septic tanks for small installations; subsurface disposal of septic-tank effluents, with emphasis on rates of application to particle size of soil; anaerobic digestion of sludge from sewage receiving phenol and formaldehyde wastes; aerobic biologic treatment of aldehyde- bearing wastes resulting from the manufacture of synthetic resins; aerobic biologic treatment of the effluent from the primary treatment of wool scouring wastes with calcium chloride, with special reference to B. O. D. and color removal; methods of treatment of waste dye liquors to remove color and B. O. D.; methods of treatment of shellfish to reduce pollution load, investigation of new methods of analysis, preparation of samples, new mediums and use of enterococci as an indicator of pollution; methods of removal of iron and manganese from the public water supplies of Lowell, Billerica and Somerset; effect of long storage on color, chemical changes and reduction of bacterial load of water; effect of particle-size gradation of filtering mediums versus effective size for the filtration of water and sewage; use of cumene hydroperoxide for reduction of B. O. D. in sewage and industrial wastes; in co-operation with the Federation of Sewage Works and United States Public Health Service, the effect of chrome salts on B. O. D. and an improved method for grease determination; method of analysis of gases produced by the anaerobic digestion of sludge; method of determination of phenols, effects of storage and inhibitors on determinations of phenols in water; effectiveness of precoat type of diatomaceous earth filters for removal of bacteria and reduction of chlorine demand in swimming pools; effect of sodium hexametophosphate on yellow brass pipe; quantitative determination of odors in the atmosphere; a rapid method for the determination of fluorides in water; use of sodium fluoride in water for the prevention of dental caries; and investigation of various commercial weed killers.

Division of Tuberculosis

The Division is at present carrying three research programs: in co-operation with the Children's Hospital, Massachusetts General Hospital and the Boston Floating Hospital, under a grant from the National Institute of Health, streptomycin treatment of children suffering from acute forms of tuberculosis, including particularly the use of streptomycin in tuberculous meningitis and miliary tuberculosis; a five-year co-operative study of BCG vaccination in student nurses and medical students by the Massachusetts Department of Public Health and the United States Public Health Service to determine the desirable preinoculation test with purified protein derivative and the optimum dosage of BCG vaccine, method of inoculation, duration of immunity and degree of protection conferred; and the study of hormonal changes in patients with carcinoma, both during and after therapy with sex hormones and related compounds, under a grant to the President and Fellows of Harvard College and Harvard School of Public Health for study from September 1, 1948, to August 31, 1949 (this work is being carried on in the laboratory of the

Department through the Pondville Cancer Hospital, where, in January, 1949, a new research laboratory for cancer, under the direction of a half-time director, was opened.

Division of Venereal Diseases

This division is evaluating the penicillin treatment of gonorrhea and syphilis, the streptomycin treatment of granuloma inguinale in varying doses to determine the most effective dose and schedules, aureomycin treatment of lymphogranuloma venereum in selected cases, and a research project to find the most effective transport mediums for gonococcus cultures.

MISCELLANY

PLASTIC SURGERY

Plastic surgery as a specialty has become well recognized. During the two world wars surgeons accumulated a wealth of experience in this field, and consequently the specialty has been greatly enlarged to the point where it is represented in organizations and publications. The newest periodical to be welcomed into the ranks of medical journalism is the *British Journal of Plastic Surgery*, inaugurated in 1948, under the editorship of A. M. Wallace, M.Sc., of the Department of Surgery of the University of Edinburgh. It is the official organ of the British Association of Plastic Surgeons. In 1946 the American group began the publication of *Plastic and Reconstructive Surgery* as the organ of the American Society of Plastic and Reconstructive Surgery, Incorporated. The typography and illustrative work of both journals are excellent.

CORRESPONDENCE

CARBON TETRACHLORIDE AND AZOTEMIA

To the Editor: In the April 7 issue of the *Journal* appears a comment by Dr. Jacob J. Silverman, of Staten Island, New York. Replying to this comment, I should give the following facts.

The patient concerned in the article on extrarenal azotemia, which appeared in the January 20 issue of the *Journal*, did indeed work in a rubber factory, and the question of any exposure to noxious agents at work was carefully considered. Not only was there communication with the factory physician about whether the patient had been exposed to noxious agents, but also one of the consultants who saw this patient was an authority on industrial diseases, and was asked to see the patient with this point particularly in mind. We were not able to obtain any evidence that he had used carbon tetrachloride or other noxious agents, and we believed that this possibility was excluded as far as possible.

James H. Townsend, M.D.

Mount Auburn Hospital
Cambridge, Massachusetts

SKIN THERMOMETERS AVAILABLE

To the Editor: In the April 7 issue of the *Journal* (on Page 587) Dr. John B. Sears, in speaking of mercurial-type skin thermometers, states: "I have found none like it manufactured in this country."

A little less than two years ago I purchased a mercurial-type skin thermometer manufactured by "RASCHER AND BETZOLD, INCORPORATED," Chicago, Illinois. This thermometer is most satisfactory, and the price is very reasonable. I believe that any surgical supply house could order it for physicians desiring one.

Robert J. Ferguson, M.D.

Ashland, Ohio

BOOKS RECEIVED

The receipt of the following books is acknowledged, and this listing must be regarded as a sufficient return for the courtesy of the sender. Books that appear to be of particular interest will be reviewed as space permits. Additional information in regard to all listed books will be gladly furnished on request.

The Metabolic Brain Diseases and Their Treatment in Military and Civilian Practice. By G. Tayleur Stockings, M.B., D.P.M. 8°, cloth, 262 pp. Baltimore: Williams and Wilkins Company, 1947. $4.50.

Peripheral Vascular Diseases: Diagnosis and treatment. By David W. Kramer, M.D., associate professor of medicine, Jefferson Medical College, assistant physician, Jefferson Hospital, chief clinical assistant, Vascular Clinic, Jefferson Hospital, visiting physician, Medical Division, and consultant on peripheral vascular disorders, Philadelphia General Hospital, attending physician, Metabolic Division, and chief of Diabetic Clinic, Jewish Hospital, attending physician and physician-in-charge, Department of Metabolic and Peripheral Vascular Disorders, St. Luke's and Children's Medical Center, and metabolist to Eagleville Sanatorium. With a foreword by Edward L. Bortz, M.D. 8°, cloth, 620 pp., with 157 illustrations. Philadelphia: F. A. Davis Company, 1948. $8.00.

NOTICES

NEW ENGLAND DIABETES ASSOCIATION

The annual meeting of the New England Diabetes Association will be held in Thayer Hall, City Hospital, Worcester, Massachusetts, on Monday, May 23, at 4 p.m.

Clinical Program

Neuropsychiatric Aspects of Diabetes. Dr. Foster L. Vibber.
Potential Diabetes. Dr. Joseph A. Lundy.
Necrotizing Papillitis in Diabetes. Dr. Edward F. Ramsdell.
Pathology of Necrotizing Papillitis. Dr. Raymond H. Goodale.
Experience with Diabetic Coma at Worcester City Hospital. Dr. Albert E. Hall.
Optimism and Diabetes. Dr. George Ballantyne.

The clinical program will be preceded by the annual business meeting including the election of officers and four directors. This meeting is planned in conjunction with the annual meeting of the Massachusetts Medical Society, May 23 to 26. The meeting will be completed in time so that councilors of the Massachusetts Medical Society can attend the Cotting supper at 6:00 p.m.

AMERICAN SOCIETY OF ELECTROENCEPHALOGRAPHY

The annual meeting of the American Society of Electroencephalography will be held at Chalfonte-Haddon Hall Hotel, Atlantic City, on Saturday, June 11 and Sunday, June 12. The meeting will begin at 10 a.m. on Saturday, and there will be a dinner for members and their guests, which ladies may attend, on Saturday night at the Chalfonte-Haddon Hall Hotel. On Sunday morning there will be a joint meeting with the American League Against Epilepsy consisting of a symposium on corticothalamic circuits. On Sunday afternoon the American League Against Epilepsy will hold the remainder of their meeting, to which members of the American Electroencephalographic Society are invited.

The business meeting of the Society, open only to members, will be held on Monday, June 13.

AMERICAN NEUROLOGICAL ASSOCIATION

The annual meeting of the American Neurological Association will be held in Atlantic City, New Jersey, on June 13, 14 and 15, with headquarters at Chalfonte-Haddon Hall.

(*Notices concluded on page xiii*)